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VASCULARIZATION AND VULNERABILITY OF THE CORNU AMMONIS IN THE OPOSSUM

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The selective vulnerability of the cornu ammonis of the human brain in various pathologic conditions, such as epilepsy, dementia paralytica, circulatory disturbances and carbon monoxide poisoning, has been attributed by Spielmeyer and others [1] to peculiarities in the local blood

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1. (*a*) Bodechtel, G.: Die Topik der Ammonshornschädigung, Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:485-535, 1930; (*b*) Zur Bedeutung des vasalen Faktors beim Hirntrauma, Deutsche Ztschr. f. Nervenh. **140**:286-307, 1936, (*c*) von Braunmühl, A.: Ueber Gehirnveränderungen bei puerperaler Eklampsie und ihre Entstehung durch Kreislaufstörungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **117**:698-727, 1928. (*d*) Hiller, F.: Ueber die krankhaften Veränderungen im Zentralnervensystem nach Kohlenoxydvergiftung, ibid. **93**:594-646, 1924; (*e*) Die Zirkulationsstörungen des Gehirns und Rückenmarks, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 11, pp. 178-465. (*f*) Hiller, F., and Grinker, R. R.: Functional Circulatory Disturbances and Organic Obstruction of the Cerebral Blood Vessels, with Contribution to the Pathology of Pertussis Eclampsia, Arch. Neurol. & Psychiat, **23**:634-655 (April) 1930. (*g*) Husler, J., and Spatz, H.: Die "Keuchhusten-Eklampsie," Ztschr. f. Kinderh. **38**:428-465, 1924. (*h*) Merritt, H. H.: Ueber Ammonshornsklerose bei der progressiven Paralyse und ihren Zusammenhang mit den sogenannten paralytischen Anfällen, Ztschr. f. d. ges. Neurol. u. Psychiat. **136**: 436-442, 1931. (*i*) Meyer, A.: Ueber die Wirkung der Kohlenoxydvergiftung auf das Zentralnervensystem, ibid. **100**:201-247, 1926. (*j*) Neubürger, K.: Ueber Ammonshornveränderungen bei apoplektischen Hirnblutungen, ibid. **111**:325-331, 1927. (*k*) Spielmeyer, W.: Zur Pathogenese örtlich elektiver Gehirnveränderungen, ibid. **99**:756-766, 1925; (*l*) Die Bedeutung der Kreislaufstörungen für die Entstehung von Gehirnkrankheiten, Naturwissenschaften **15**:531-537, 1927; (*m*) Die Pathogenese des epileptischen Krampfes, Ztschr. f. d. ges. Neurol. u. Psychiat. **109**:501-536, 1927. (*n*) Kreislaufstörungen und Psychosen, ibid. **123**: 536-573, 1930; (*o*) The significance of Local Factors for Electivity in Central

(Footnote continued on next page)

supply.[2] These investigators brought forward various explanations to show in what way the vascularization of the region is the decisive factor in this vulnerability.

1. The vascularization of the cornu ammonis is poor (Spielmeyer and Uchimura [3]). Its margin of safety is, therefore, smaller than that of other parts of the brain. Thus, in a case of circulatory insufficiency the nerve cells are inadequately supplied and disintegrate before the cells in other parts of the brain, where the capillary bed is richer, begin to suffer.

2. The cornu ammonis, particularly the most vulnerable area known as Sommer's sector, is said to be supplied by a blood vessel (Uchimura [4]), or rather by blood vessels (Altschul [5]), the so-called septal vessels, which more than any others in the human brain have the character of end arteries.[6] Hence the area supplied by these vessels receives its blood only from this source, and little or nothing from neighboring vessels by way of anastomoses. Accordingly, in the case of a vascular crisis affecting these septal vessels, the nerve cells supplied by them succumb earlier than do those in regions where more exchange of blood between neighboring vascular units is possible.

3. Spielmeyer and his co-workers furthermore expressed the idea that in cases of circulatory disturbances the septal vessels of the cornu ammonis are more likely to fail in supplying the nerve tissue because they are predisposed to spasms or to stasis, as their course from the hippocampal artery to the region of their capillary distribution is long and twisted. This twisted course was said to be caused by the complicated ontogenetic and phylogenetic involution of the archicortex that results in the formation of the cornu ammonis.

Nervous System Disease Processes, Medicine **10**:243-256, 1931. (*p*) Weimann, W.: Gehirnveränderungen bei akuter und chronischer Morphiumvergiftung, Ztschr. f. d. ges. Neurol. u. Psychiat. **105**:704-751, 1926.

2. The pathoklisis theory of C. and O. Vogt (Sitz und Wesen der Krankheiten im Lichte der topistischen Hirnforschung und des Variierens der Tiere, J. f. Psychol. u. Neurol. **47**:237-457, 1937) is not discussed, since there is no evidence that their point of view applies to the material presented here.

3. Spielmeyer, W.: The Anatomic Substratum of the Convulsive State, Arch. Neurol. & Psychiat. **23**:869-875 (May) 1930. Uchimura, J.: Zur Pathogenese der örtlich elektiven Ammonshornerkrankung, Ztschr. f. d. ges. Neurol. u. Psychiat. **114**:567-601, 1928.

4. Uchimura, J.: Ueber die Gefässversorgung des Ammonshornes, Ztschr. f. d. ges. Neurol. u. Psychiat. **112**:1-19, 1928.

5. Altschul, R.: Die Blutgefässverteilung im Ammonshorn, Ztschr. f. d. ges. Neurol. u. Psychiat. **163**:634-642, 1938.

6. For the question of cerebral end arteries see Cobb, S.: The Cerebral Circulation: XIII. The Question of "End-Arteries" of the Brain and the Mechanism of Infarction, Arch. Neurol & Psychiat. **25**:273-280 (Feb.) 1931.

The different investigators were inclined to lay more emphasis on one or the other of these three points, and not rarely to combine them in various ways. The long and twisted course of the septal arteries, for instance, was assumed to facilitate spasmodic constriction, and the poor development of anastomoses to hinder mutual compensation of the blood supplies of the sector of Sommer and the neighboring areas during such vasoconstriction. In a case of carbon monoxide poisoning, for example, in which localized lesions occur in the cornu ammonis, the partial lack of oxygen in the blood and the poisonous effect of the carbon monoxide are more effective in an area where the vascularization is poor and where anastomoses are rare than in other regions where various sources of blood supply are well pooled and the capillary bed is dense.

Against these theories and their combination a number of objections can be raised. Thus, a deficiency of vascular supply, as judged by the density of the capillary bed, has not been observed. The capillarization of the cornu ammonis has not been found poorer than that of other parts of the brain of comparable structure, either in man (Hiller [1d]) or in the rat (Craigie [7]). Cobb [8] found that in the rabbit the lamina pyramidalis of the cornu ammonis is more vascular than is the cell layer of the gyrus dentatus. The length of the septal vessels is, furthermore, not so excessive that it could possibly play a role. Other vessels in the brain are longer, and the areas which they supply show no particular vulnerability. It is mere conjecture to assert that the twisted course of a vessel favors spasmodic constriction, and no experimental proof for this hypothesis is thus far available. No investigation has been carried out as to whether brain tissue vascularized by end arteries suffers more from disturbances in the circulation of the blood, such as are caused by carbon monoxide poisoning, than that supplied by a vascular system of the network type. The latter point constitutes the main question in this connection, as it represents a problem of general interest concerning the vascularization of the central nervous system.

Since, on the other hand, the problem of the vulnerability of the cornu ammonis is of significance in neuropathology and is interesting also from the anatomic and the physiologic points of view, it seems worth while to submit observations based on experimental investigation in place of assumptions such as those already outlined. An opportunity to do so is afforded by the unusual vascular pattern of the brain of the

7. Craigie, E. H.: The Vascular Supply of the Archicortex of the Rat: I. The Albino Rat (Mus Norvegicus Albinus), J. Comp. Neurol. **51**:1-11, 1930; II. The Albino Rat at Birth, ibid. **52**:353-357, 1931; III. The Wild Norway Rat (Mus Norvegicus) in Comparison with the Albino, ibid. **52**:359-364, 1931; IV. Inbred Albino Rats, ibid. **55**:443-451, 1932.

8. Cobb, S.: The Cerebral Circulation: VIII. A Quantitative Study of the Capillaries in the Hippocampus, Arch. Surg. **18**:1200-1209 (April) 1929.

opossum, as recently described by Wislocki and Campbell.[9] Their discovery made available a laboratory animal with a cerebral blood supply of purely end arterial type, in contrast to the network patterns of all other mammals heretofore studied. The question formulated in the foregoing discussion concerning the effect of circulatory disturbances on brain tissue vascularized by a network system as compared with one supplied by end arteries can therefore be studied experimentally. An investigation of this kind has been carried out and is reported here. The opossum was used as the experimental animal and carbon monoxide as a drug which is known to cause selective lesions in the human brain. The results obtained not only seem to contribute further information regarding the functional significance of the capillary bed of the opossum's brain [10] but may also be of use in the investigation of the problem of selective vulnerability in the human brain.

MATERIAL AND METHODS

In the experiments to be reported 31 opossums were subjected to poisoning with illuminating gas. A first series of experiments on 13 opossums was conducted in Chicago and a second on 18 opossums in New York. The series differed in several respects.

The analysis of the illuminating gas used in Chicago [11] is as follows:

	By Volume Per Cent
Carbon dioxide	0.9
Heavy hydrocarbons, such as ethylene and propylene	1.9
Oxygen	0.3
Carbon monoxide	2.3
Hydrogen	25.5
Methane	55.5
Lighter hydrocarbons, such as ethane and butane	6.8
Nitrogen	6.8
Sulfur	Trace

In the series in Chicago [12] the animal was kept in a basket, the bottom of which was covered with wood shavings, and a large bell jar was placed over the animal. Through a rubber tube illuminating gas was admitted into the jar until the animal showed signs of acute poisoning, after five to ten minutes. The symptoms were unconsciousness, rigidity of the body, spasmodic convulsions, passing of feces and urine and vomiting. The animal was then quickly removed from the bell jar and allowed to breathe fresh air. The tonic spasm of the thoracic muscles had to be overcome by artificial respiration, which was simply administered by forcible compression and extension of the thorax until spontaneous respiratory movements returned. Under the conditions described recovery

9. Wislocki, G. B., and Campbell, A. C. P.: The Unusual Manner of Vascularization of the Brain of the Opossum (Didelphys Virginiana), Anat. Rec. **67**:177-191, 1937.

10. Scharrer, E.: The Functional Significance of the Capillary Bed in the Brain of the Opossum, Anat. Rec. **75**:319-340, 1939.

11. The Peoples Gas Light and Coke Company furnished the analysis of this gas.

12. Dr. D. Clark assisted in this work.

may be rapid, taking only a few minutes, or hours may pass, until convulsions cease or death occurs. The animals which were restored to normality were allowed pauses of from five minutes to several days until the next poisoning was produced. In only 3 of the Chicago series of 13 opossums (cases 9, 21 and 34) were lesions observed in the cornu ammonis on histologic examination. In the other 10 opossums the cornu ammonis was found either fully intact or with only slight loss of cells in a small sector of the pyramidal layer, as in case 35.

The analysis of the illuminating gas used in New York[13] is as follows:

	By Volume Per Cent
Carbon dioxide	3.4
Ethylene and benzine	6.6
Carbon monoxide	16.6
Hydrogen	35.2
Methane	20.5
Nitrogen	16.7
Oxygen	1.0

The animals were kept in their cages, which were placed under a chemical hood. The amount of illuminating gas mixed with the air and sucked through the hood was regulated in a way so that the animals were kept in a deep coma interrupted by fits of clonic-tonic spasms, vomiting and other symptoms. They were subjected to this treatment in an atmosphere of high carbon monoxide concentration for several hours per day over a number of days.

The poisoning produced in Chicago was, therefore, much milder than that produced in New York, with respect to the carbon monoxide content of the illuminating gas as well as the time during which the animals were under the influence of carbon monoxide. Of the 18 opossums poisoned in New York the majority died during the first hours of administration of the gas. Five animals (cases 44, 46, 52, 56 and 58) survived repeated poisonings and showed lesions in the cornu ammonis.

Animals that died during the poisoning or were intentionally killed with illuminating gas were perfused with fixative (95 per cent alcohol; Zenker's solution with formaldehyde) or the brain was quickly removed and fixed by immersion. Some animals were given injections of india ink and gelatin. All the brains were embedded in pyroxylin (nitrocellulose). The brains which were not injected were cut serially in sections 20 microns thick and stained with thionin or toluidine blue (Nissl preparations), iron hematoxylin, Foot's modification of Masson's trichrome stain and other methods. The injected brains were cut in series of alternating sections 20 microns thick, stained by Nissl's method, and 200 microns thick, mounted unstained. There were, in addition, serial sections of normal brains available for comparison. The vascularization of the cornu ammonis was studied by dissection, under the binocular microscope, of brains in which the blood vessels had been injected with prussian blue and gelatin or carmine and gelatin, and in a complete series of a brain which had been injected with carmine and gelatin according to the method of Bensley and Bensley.[14] In this series a section 20 microns thick stained by Nissl's method and a section 200 microns thick unstained were mounted together on one slide in the sequence in which they had been cut alternately.

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13. The Consolidated Edison Company of New York, Inc., furnished the analysis of this gas.

14. Bensley, R. R., and Bensley, S. H.: Handbook of Histological and Cytological Technique, Chicago, University of Chicago Press, 1938, p. 152.

EFFECT OF CARBON MONOXIDE ON THE CORNU AMMONIS OF THE OPOSSUM

On examination of serial sections of brains of opossums that had been subjected to poisoning by carbon monoxide, one is struck by the selective effect of the gas on the cornu ammonis, in particular on the cortex ammonis proper (pyramidal layer),[15] as shown in figure 1. Poisoning by carbon monoxide results in ischemic lesions, the main feature of which is the disappearance of the nerve cells. The vascular and glial reactions vary in different cases according

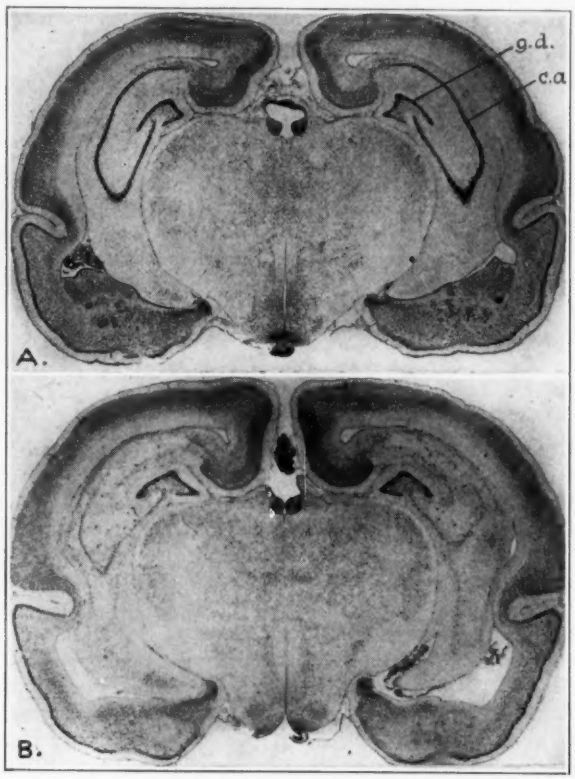

Fig. 1.—Effect of carbon monoxide poisoning on the cornu ammonis of the opossum. *A,* cross section through the brain of a normal opossum. *g. d.* indicates the gyrus dentatus (fascia dentata), and *c. a.*, the cortex ammonis (pyramidal layer). *B,* cross section through the brain of opossum 9, which had been subjected to repeated carbon monoxide poisoning. The cortex ammonis is necrotic. The tissue was fixed in 95 per cent alcohol, embedded in pyroxylin (nitrocellulose), cut at a thickness of 20 microns and stained by Nissl's method. × 15.

to the age of the process. Here the chief concern is with the localization and extent of the lesions.

15. For a description of the cornu ammonis of the opossum's brain see Loo, Y. T.: The Forebrain of the Opossum, Didelphis Virginiana: I. Gross Anatomy. J. Comp. Neurol. **51**:13-64, 1930; II. Histology, ibid. **52**:1-148, 1931.

In 3 cases (21, 34 and 9) the lesions were symmetric, and therefore only one half of the brain is shown in the diagrammatic figures. In case 21 the animal had been exposed to illuminating gas six times in Chicago, with the method described. The poisoning was carried out over a period of twenty days, one treatment being given on the first, the tenth, the twelfth, the thirteenth, the nineteenth and the twentieth day. The animal died the day after the last administration. The nearly symmetric lesions occupied only a narrow strip in the dorsal part of the cortex ammonis but were observed in a number of sections, as indicated in figure 2*A*. Since no lesions were seen in some cases in which the same or even a higher number of poisonings had been produced, the six periods of poisoning in case 21 apparently represent a minimum under which no irreversible damage of the brain occurs.

A more extensive lesion, which is exactly symmetric, is shown in case 34 (fig. 2 *B*). The animal had been poisoned by the same method as that used for opossum 21; gas was given eight times over a period of seven days. There had been one poisoning on the first, the second and the third day, two poisonings on the fourth day, one on the fifth, two on the sixth and one on the seventh. A second poisoning on the seventh day ended with the death of the animal, the brain of which was then immediately fixed.

A third example is shown in case 9 (fig. 2 *C*). The animal was treated in Chicago over a period of thirty-four days, having been poisoned twice on the first and the seventh day and once on the twenty-fifth, the twenty-sixth, the twenty-seventh and the twenty-eighth day. It was killed with gas on the thirty-fourth day. Softening of the cornu ammonis was noted even macroscopically in the cross section of the fresh brain. Histologic study revealed an extensive symmetric lesion.

The perfect symmetry of the lesions in most of these cases is well demonstrated in case 44 (fig. 3 *A*), in which the pathologic changes were extensive, involving also a large part of the fascia dentata, which usually remains intact. This animal had been subjected to poisoning by the New York method over a period of five days. On the first day it was kept in the gas-filled chemical hood for three and one-half hours, and on the second and the third days for six and one-half hours each. It died on the fifth day when another poisoning was attempted.

Cases in which there were asymmetric lesions are much rarer. Of this type, case 46 (fig. 3 *B*) may serve as an example. Poisoning had been produced over a period of four days by the New York method. On the first day the animal was in the gas chamber for five and one-half hours and on the second day for six and one-half hours, and died on the fourth day when again put under gas.

In summary, it may be stated that carbon monoxide poisoning in the opossum results in ischemic lesions of the cornu ammonis, the main features of which are selectivity and symmetry in the majority of the cases.

As regards the histologic changes in the lesions, the extent of which has just been outlined, little need be said. They are those of the typical ischemic lesions brought about by anoxemia, as described by various authors. Figures 4 and 5 illustrate one phase, i.e., the paling of the nerve cells (*Erbleichung*, according to Spielmeyer). The cells can still be seen faintly, but they do not stain. The process has affected the cortex ammonis in its entire length and a small part of the gyrus dentatus. Attention is again called to the perfect symmetry in the

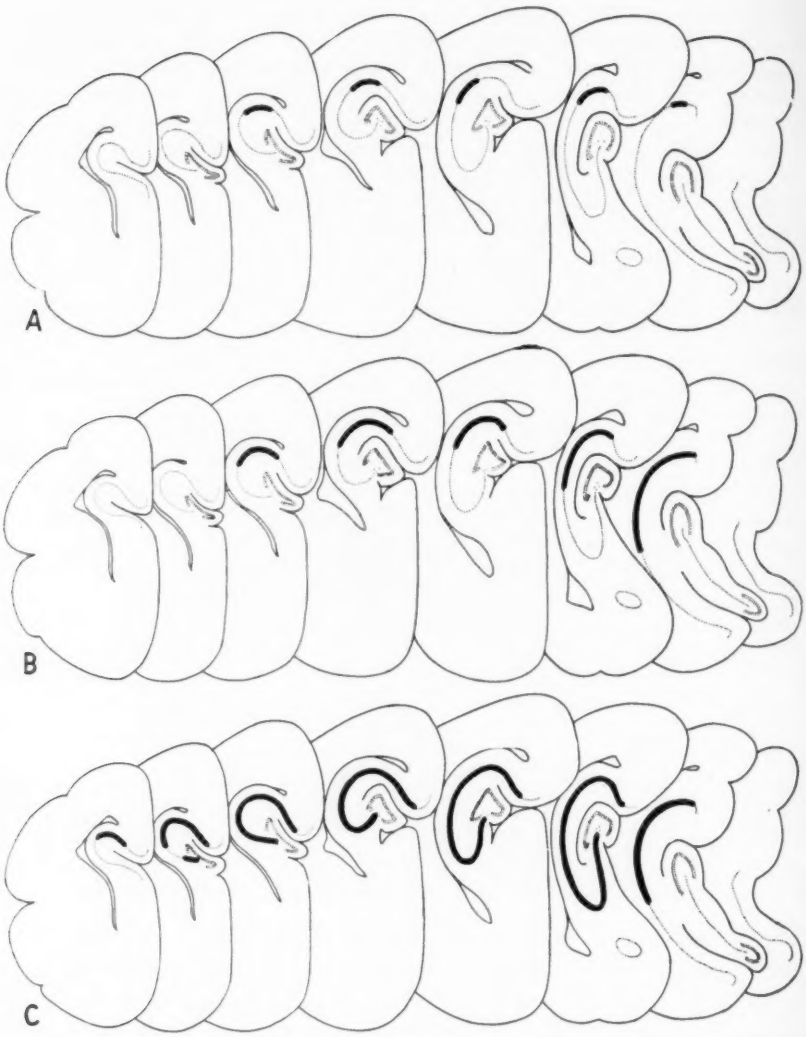

Fig. 2.—Schematic drawing of series of cross sections through the brains of opossums which had undergone carbon monoxide poisoning. The lesion in the cornu ammonis is indicated by a heavy black line; the intact cells of the cortex ammonis and gyrus dentatus are represented by dots. Since the lesions are symmetric, only one hemisphere need be shown. *A*, opossum 21 with a small lesion; *B*, opossum 34, with a somewhat more extensive lesion, and *C*, opossum 9, with a still larger lesion. Note that the gyrus dentatus is not affected in any of the 3 cases.

extent of the lesions. The corresponding injected preparation shows that the blood vessels are still open to circulation, but they are perhaps no longer normal, as indicated by frequent small extravasates of the injection fluid, attributable to ruptures of the walls of the vessels. The opossum (case 58) the brain of which is shown in figures 4 and 5 had been subjected to severe poisoning over eleven days, with the method used in New York. The animal had spent one hour in the gas chamber on the first day, six and one-half hours on the second day, five hours on the third day, four hours on the fourth day, five hours on the seventh day, seven and one-half hours on the eighth day and eight hours each on

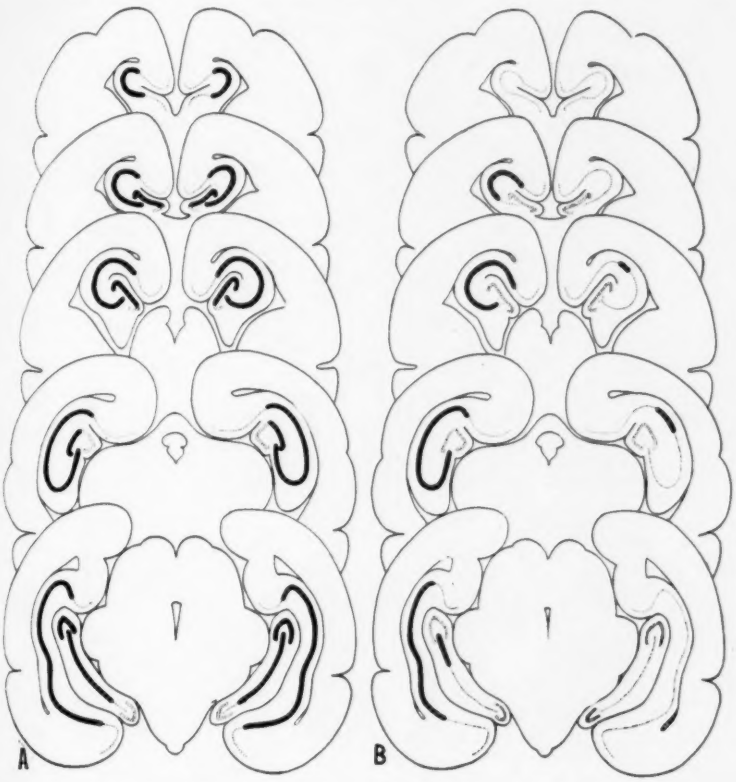

Fig. 3.—*A*, opossum 44, with almost complete destruction of the cornu ammonis and involvement also of the gyrus dentatus. Note the perfect symmetry of the lesions. *B*, opossum 46, representing one of the rarer cases of asymmetry of the lesions.

the ninth, tenth and eleventh days. It was killed with gas on the twelfth day. The lesions obviously did not develop sufficiently early to allow time for transformation of the ischemic necrosis of the nerve cells into softening. For comparison there are shown sections, in figures 6 and 7, case 56, in which the stage of fully developed softening had been reached. The carbon monoxide treatment had been extended over more than twice the time given in case 58, namely twenty-five days. Fifteen poisonings of five to eight hours each were produced.

Attention is called to the fact that even this severe poisoning did not affect parts of the brain other than the cortex ammonis. Here the pathologic process is marked by glial and vascular reactions, as shown in the Nissl preparation. The blood vessels were occluded by proliferation of the endothelium and were, therefore, not filled in the injected preparation. The vascular reaction undoubtedly represents a later phase in the development of the lesion. The glial reaction gradually leads to the formation of a scar, which in the case of human epilepsy is known as sclerosis of the cornu ammonis. In case 56 transformation of the softening into a sclerotic glial scar is already under way.

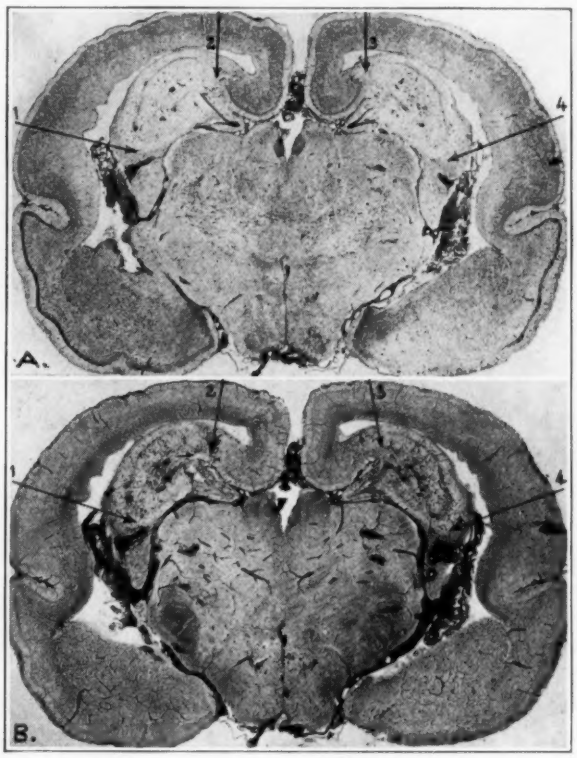

Fig. 4.—Ischemic lesion in the brain at an early stage, showing paling of the nerve cells (opossum 58). *A*, section stained by Nissl's method and cut 20 microns in thickness. *B*, unstained section, 200 microns in thickness, of brain injected with india ink and gelatin. *A* and *B* represent adjacent sections. The affected cornu ammonis extends between arrows *1* and *2* and *3* and *4*, respectively. × 1.5.

Whereas in the majority of these cases striking symmetry of the lesions and unquestionable limitation of the pathologic process to the cornu ammonis were displayed, there were occasional instances in which asymmetric necrosis or foci of ischemia had developed in other parts of the brain in addition to the lesions in the cornu ammonis. As an example, case 52 is illustrated in figure 8. In this case, furthermore, processes of different ages are shown. The animal had

been subjected to poisoning in New York over twenty-nine days, during which it was in the gas chamber eighteen times, each time for five to eight hours. The first lesions must have developed in the dorsal parts of the cortex ammonis (fig. 8, in the areas between arrows 2 and 3 and 5 and 6, respectively). In this location lesions occurred frequently in cases of milder poisonings (figs. 2 and 3). In opossum 52 the earlier lesions developed into symmetric areas of softening. Later ischemia occurred on one side in the ventral segment of the cortex ammonis, involving also a small part of the gyrus dentatus. This lesion was in the first stage of necrosis, characterized by loss of stainability of the nerve cells. Proliferation of glial and vascular elements had not yet taken place. In the other hemisphere this segment of the cortex ammonis was still fully intact.

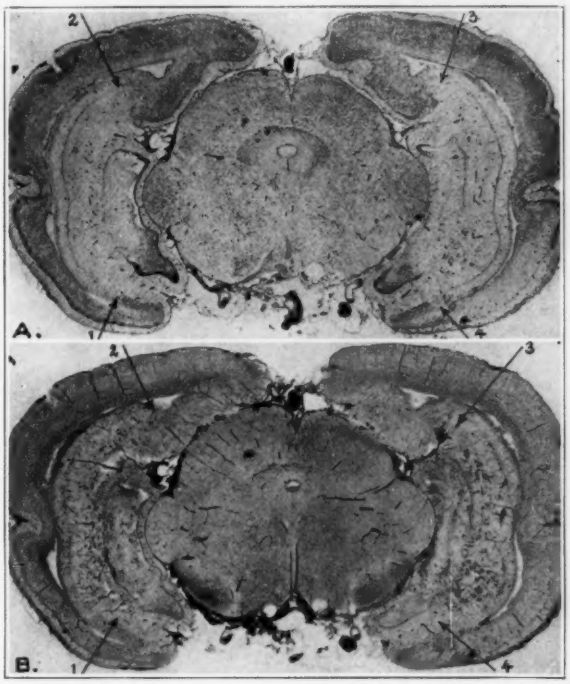

Fig. 5.—Sections from the same brain as those shown in figure 4, but farther caudal.

But the one hemisphere suffered not only in respect to the cornu ammonis; there were, in addition, an ischemic lesion in the paleocortex and in the neocortex, respectively. It cannot be stated definitely why in this case the one hemisphere was so much more vulnerable than the other.

Another observation needs elucidation, i.e., the fact that sometimes the most severe poisoning is without the slightest effect. Cases 41 and 44 may serve as examples. As shown in figure 3, there had developed in opossum 44 a very extensive lesion, while in opossum 41, which had been in the gas chamber with opossum 44 for the same length of time, the cornu ammonis was fully intact. The blood vessels of the cornu ammonis in opossum 41 showed no signs of pathologic changes, and no loss of cells could be discovered in the pyramidal layer.

From what has been reported here, it is evident that the ischemic lesions occurring in the cornu ammonis of the opossum do not differ histologically from those described in human beings (Hiller [1d]) or in other mammals after experimental carbon monoxide poisoning (Meyer [16]). The same stages were observed in the animals as in man,

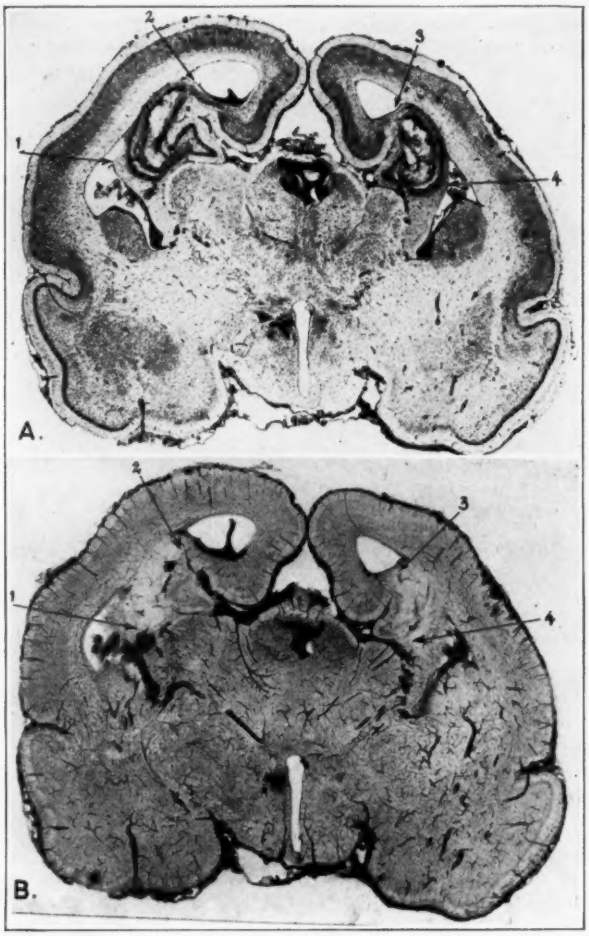

Fig. 6.—Ischemic lesion in the stage of softening (opossum 56). Glial and vascular elements are proliferating. Endarteritis of the vessels in the cornu ammonis prevented their filling in the injected preparation. For technic see figure 4.

i.e., ischemia with loss of stainability of the nerve cells as the initial step in a series of processes which leads to the softening and finally to the sclerosis of the affected area.

16. Meyer, A.: Experimentelle Erfahrungen über die Kohlenoxydvergiftung des Zentralnervensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. **112**:187-212, 1928.

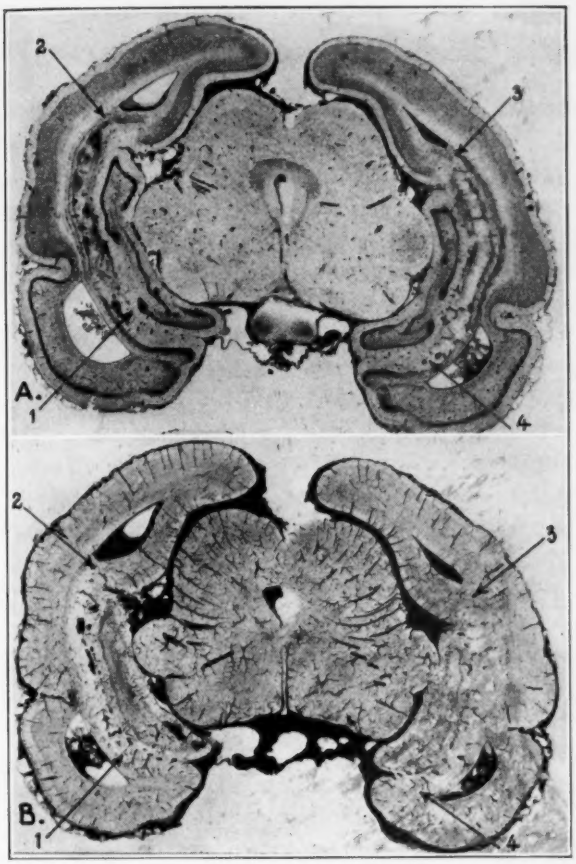

Fig. 7.—Sections from the same brain as those shown in figure 6, but farther caudal.

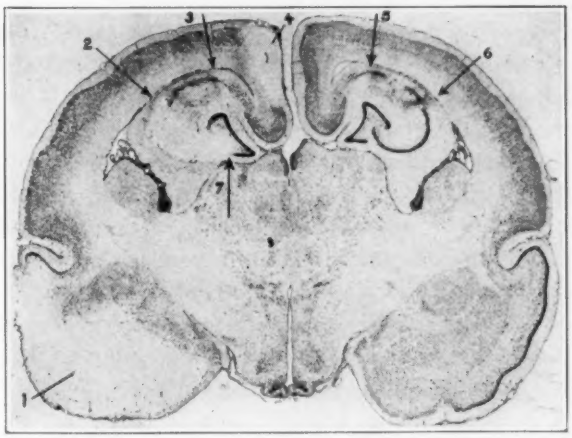

Fig. 8.—Cross section through the brain of opossum 52. The oldest symmetric lesions in the stage of softening lie between arrows *2* and *3* and *5* and *6*. In addition, there is fresh asymmetric lesion in one cornu ammonis between arrows *2* and *7*. Fresh lesions in the first stage of necrosis are indicated by *1* in the paleocortex and by *4* in the neocortex. Nissl's preparation; × 6.

TENTATIVE EXPLANATION OF SELECTIVE VULNERABILITY IN THE OPOSSUM

There are various ways of explaining the vulnerability of the cornu ammonis in man; some of them have been briefly outlined in the introduction, and it will next be considered whether one of them fits the case of the opossum.

It has been suggested that the cornu ammonis may be poorly vascularized and may, therefore, succumb in the case of circulatory insufficiency before other regions of the brain in which the vascularization is richer. It has already been remarked that neither in man nor in the lower mammals studied thus far has inadequate vascularization actually been observed. This holds true also for the opossum, in which the cornu ammonis has by no means a poor supply of blood.

There exists also the possibility that carbon monoxide has a specific poisonous effect on the endothelial and adventitial cells of the blood vessels and that the vessels of the cornu ammonis are more sensitive in this respect than are those of other regions of the brain. Repeated poisonings would then result in proliferation of these elements, to the effect that the vessels become narrower, allowing less blood to circulate through them, and their walls become thicker, which may decrease their permeability. The nerve cells thus gradually die for lack of oxygen and nutriments. A process of this character might be reconstructed from an exclusive study of fully developed lesions. There, indeed, the blood vessels are not rarely conspicuous as solid bands of cells, their lumen filled with endothelial cells, some of which display mitotic figures; and they are surrounded by a sheath of adventitial and glial elements in all stages of proliferation. However, in cases of the early stages or cases in which no lesion had developed at the time the animal was killed, despite long-repeated poisonings (cases 41 and 55), no initial stages of endarteritis and periarteritis have been observed. The lesions in the opossum, rather, correspond to the stages in the development of anoxemic lesions in the human brain, which Spielmeyer [17] has described. The first stage shows atrophy of the nerve cells (necrobiosis and *Erbleichung*), without a vascular reaction. In that case the blood vessels can still be filled with injection fluid. The processes affecting the blood vessels and the glia are clearly of secondary nature and are not pathognomonic for carbon monoxide poisoning. They lead to softening of the nerve tissue and finally to the formation of a sclerotic scar, in the same way as in any ischemic lesion in the human brain. It may be concluded, therefore, that the pathologic process in the opossum starts in the cornu ammonis with ischemia of the nerve cells. The

17. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1922.

endarteritic and periarteritic changes in the vessels follow, but do not cause, the disintegration of the nerve cells.

The ischemia could also be caused by thrombotic or embolic occlusion of the vessels of the cornu ammonis. These changes, however, have not been observed as a result of carbon monoxide poisoning in the higher mammals and in man (Hiller [1d] and [e]), nor was there any indication of their occurrence in the opossum. Functional occlusion caused by spasms, however, was assumed by Spielmeyer and his school to play a major role in man, particularly in cases of epilepsy. The question of such spasms is still under discussion, and the observations made in the opossum do not contribute anything of value toward the solution of this problem. If it is possible that angiospasms can continue for so long that the resulting occlusion of the vessel causes anemia and an irreversible ischemic lesion,[18] the limitation of such spasms to the cornu ammonis, as in the case of the opossum, needs explanation. In regard to the cornu ammonis in man, this selective localization has been related to the long and twisted course of the septal vessels, which in turn is said to be a consequence of the complicated involution of the archicortex taking place phylogenetically and ontogenetically. In the opossum the branches supplying the cortex ammonis do not appear to be longer or more twisted than many other vessels in the brain, where the area of supply has never been observed to suffer from carbon monoxide poisoning. It is true that the branches of the hippocampal artery curve around the gyrus dentatus to reach their destination (fig. 10), but this course can hardly be called twisted, and it seems even more difficult to demonstrate how this or any more twisted course would facilitate spasms under the influence of carbon monoxide. The same statement applies to the length of the vessels in question. Their length is not excessive as compared with other vessels of the brain, nor is there any evidence that the length of a vessel is correlated with its readiness to undergo spasms.

One of the major points in the various theories concerning vulnerability of the cornu ammonis in man has been the quasiterminal character of the septal vessels. From the description previously given, however, it is evident that end arteries as such do not play a major role in the vulnerability of the cornu ammonis. If end arteries were so highly unfavorable in the case of gas poisoning, it would be expected that in the opossum lesions would be distributed over the brain and spinal cord, since the whole central nervous system of the opossum

18. Cobb, S.: The Cerebral Circulation: IX. The Relationship of the Cervical Sympathetic Nerves to Cerebral Blood Supply, Am. J. M. Sc. **178**:528-536, 1929.

is supplied exclusively by true end arteries.[19] This is not the case, however, for only the cornu ammonis displays marked vulnerability.

Apparently, none of the hypotheses put forward to explain the vulnerability of the cornu ammonis in man fits the case in the opossum in such a way that it might be borrowed advantageously. It has been attempted, therefore, to explain the vulnerability of the cornu ammonis in the opossum independently, i. e., with regard to such factors as are known and clearly demonstrable.

Only two such factors were found, but they proved to be sufficient. The one is a rather simple anatomic difference between the vascularization of the cornu ammonis and the rest of the brain of the opossum. Whereas the blood vessels in all parts of the brain thus far studied divide more or less dichotomically, in the cornu ammonis the branches for the nerve tissue start from the hippocampal artery in a rakelike fashion (figs. 9 and 10). This difference is indeed the only one that can be clearly demonstrated. The question is: In what way can this difference alter the action of carbon monoxide on the nerve tissue so that the cornu ammonis appears to be more vulnerable than other parts of the brain?

In fact, all the physiologic effects of carbon monoxide poisoning can act equally on all nerve cells by means of the vascular system. Thus the lack of oxygen, the asserted poisonous action on the nerve cells[20] and the effect on the blood vessels, either through paralysis, with resulting atonia and dilatation, or through spasmodic constriction, are likely to affect the vessels all over the brain to the same extent, no matter how they give off their branches. There is, however, one effect of carbon monoxide which, as a rule, is not mentioned in discussion of the vulnerability of the cornu ammonis, i. e., the decrease in the velocity of the flow of blood through the cerebral vessels.

The velocity of flow is decreased in carbon monoxide poisoning for two reasons, which are interrelated: 1. Carbon monoxide causes dilatation of the cerebral blood vessels, as recorded in intravitam observations of the blood vessels on the surface of the brains of experimental animals. This dilatation, particularly of the veins, is also always observed in sections of brains of animals that have been killed with illuminating gas and of opossums that have undergone carbon monoxide poisoning. Since the increase in the diameter of a tube causes a decrease in the velocity of flow through the tube, the blood flow will be slowed

19. (*a*) Scharrer, E.: Ueber cerebrale Endarterien, Ztschr. f. d. ges. Neurol. u. Psychiat. **162**:401-410, 1938; (*b*) footnote 10. (*c*) Wislocki and Campbell.[9]

20. Mitolo, M.: L'azione centrale dell' ossido di carbonio, Arch. di fisiol. **27**:323-343, 1929; Ulteriori ricerche sull' azione centrale dell' ossido di carbonio, ibid. **29**:318-325, 1931.

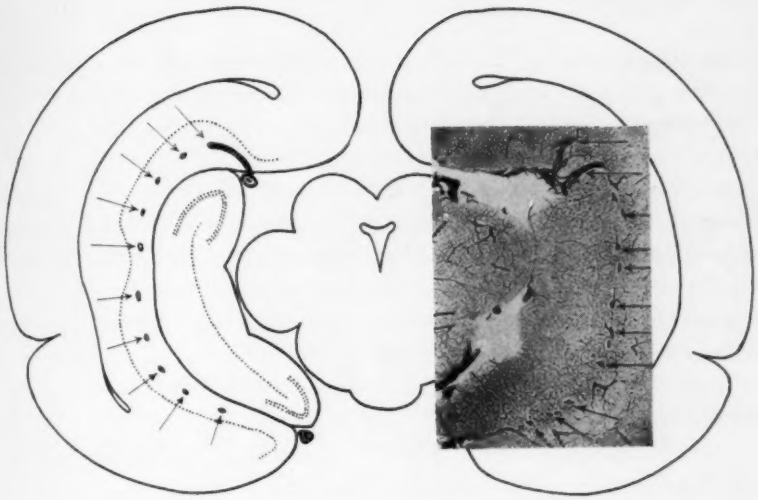

Fig. 9.—Photodiagram showing the position and vascularization of the cornu ammonis in a cross section of an opossum's brain. The branches supplying the cornu ammonis are all seen in cross sections (indicated by arrows); only the two upper ones are cut longitudinally. For explanation of this arrangement see figure 10.

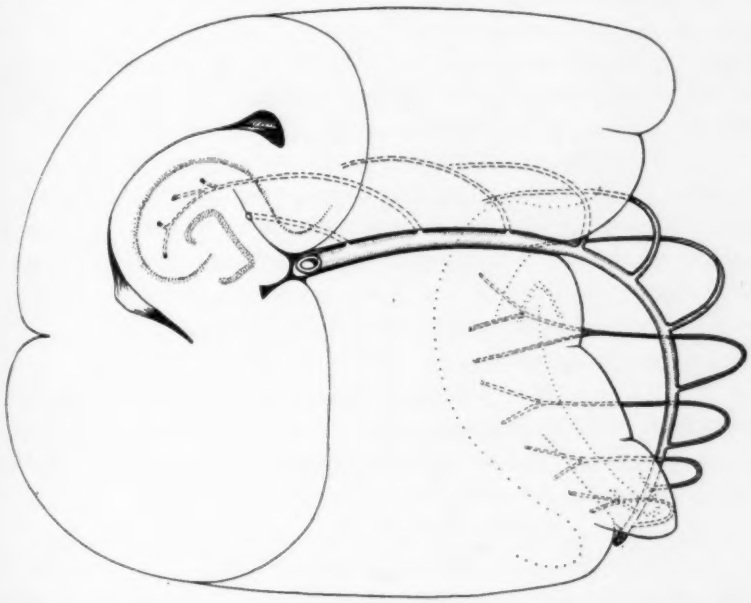

Fig. 10.—Diagrammatic reconstruction of the principle of the vascularization of the cornu ammonis in the opossum. The branches supplying the cornu ammonis leave the main vessel in a rakelike fashion. The right hemisphere of the opossum's brain is shown cut in two planes, which can be identified with planes of sections shown in previous figures. The posterior plane is supposed to be the same as that of the cross section shown in the preceding figure.

in the dilated vessels. 2. Sufficiently rapid circulation of the blood in the brain could be maintained, however, if an increase in the systemic blood pressure would compensate for the vascular dilatation in the brain. But the systemic blood pressure drops because of the general dilatation of the vessels in the whole body and the effect of the carbon monoxide on the heart.[21] Thus, the decrease in the blood pressure in the brain, attributable to the local dilatation of the cerebral blood vessels, and the drop in the systemic blood pressure combine in such a way as to make compensation impossible. A considerable decrease of velocity in the blood flow must be the result.

It appears clear, however, that in order that the nerve cells may survive the low oxygen content of the blood which results from the conversion of oxyhemoglobin to carbon monoxide hemoglobin,[22] the blood must flow in the vessels with a certain minimal speed so as to provide a minimal quantity of oxygen for the nerve tissue.

The criticism may be made that under normal conditions the blood flow is slowed considerably in the capillaries, as compared with its velocity in the arteries and veins. This is necessary in order to give the blood corpuscles opportunity to exchange the blood gases. But there exists an optimal speed at which this exchange functions best, which is not necessarily the same in different organs. It is true that in such organs as are accessible for intravitam observation of capillaries (tongue of the frog, for example) it has been observed that under certain conditions the velocity of the blood flow can be diminished in the capillaries to almost zero without causing damage to the tissue. It would be unsafe, however, to assume that something similar can take place in the brain. There is every indication that nerve tissue cannot tolerate too sluggish a blood flow and needs a continuous rapid supply. Its margin of safety with regard to the volume of blood per unit of time and the percentage of oxygen carried by the blood is much smaller than that of any other organ. The reasoning proposed here for the explanation of the vulnerability of the cornu ammonis is thought to be correct, therefore, even if it may not apply to other organs for which direct observations are available.

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21. Rigler, R., and Rothberger, C. J.: Die Pharmakologie der Gefässe und des Kreislaufes, in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1927, vol. 7, sect. 2, pt. 2, pp. 1050-1051. Kayser, H. W.: Der Einfluss des Kohlenoxyds auf vasomotorische Reaktionen, Arch. f. exper. Path. u. Pharmakol. **192**:625-633, 1939.

22. Henderson, Y., and Haggard, H. W.: Noxious Gases and the Principles of Respiration Influencing Their Action, American Chemical Society Monograph Series, New York, Chemical Catalog Company, Inc., 1927, p. 105.

As illustrated diagrammatically in figure 11, a decrease in blood pressure and in the velocity of blood flow, distributed more or less equally over all branches of a dichotomically dividing vessel, permits the circulation to go on in all branches, though at a slower rate. As long as the saturation of the blood with carbon monoxide is not too high and the poisoning is not extended over too long a period, the nerve cells survive; this was actually observed in the larger part of the brain of the opossum. The effect on the cornu ammonis, however, is different, as the slowing of the blood flow is not distributed equally in the system in which the branches do not divide dichotomically, but start off from the main artery one after the other. When one considers the problem schematically as a simple one of hydrodynamics in its purely physical aspect, while fully keeping in mind that many additional factors play their roles in bringing about the ultimate result, one sees that the principles governing the flow of a liquid through a system of tubes apply to a pattern such as this. These principles are amply discussed in textbooks of physiology—for instance, that of Best and Taylor.[23] It is to be assumed that there exists a critical level of blood pressure, below which blood flow becomes so slow that the amount of oxygen available is insufficient to maintain the nerve cells alive. Possibly a slow blood flow also enhances the poisonous effects of the carbon monoxide, such as the inhibition of respiratory enzymes.[24] From figure 11 it seems evident that irreversible damage of the nerve tissue is likely to occur earlier in the cornu ammonis, on the basis of its vascular pattern, than in other parts of the brain, because blood pressure may fall unequally in different parts of its vascular system and may thus drop below the critical level when in the rest of the brain there are still maintained a blood pressure and consequently a velocity of flow that are sufficient to keep the nerve tissue intact.

As is to be expected, a mechanism of this kind would also explain the often striking symmetry of the lesions in the two hemispheres of the brain, since the same physical principle applies to systems of corresponding structure on the two sides. Furthermore, the outspoken individual differences in the reactions of the opossum to carbon monoxide poisoning, which have been observed also in other mammals and in man —in that the same volume of gas over the same length of time is fatal for one subject whereas another suffers but little—could be understood equally well as a matter of blood pressure, which varies greatly from one subject to another according to age and other factors.

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23. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, Baltimore, William Wood & Company, 1937, p. 180-184.

24. Warburg, O.: Ueber Kohlenoxydwirkung ohne Hämoglobin und einige Eigenschaften des Atmungsfermentes, Naturwissenschaften **15**:546, 1927.

Finally, it seems understandable from a study of figure 11 why lesions may occasionally occur also in parts of the opossum's brain other than the cornu ammonis. There need take place only a drop in blood pressure beneath the critical level in any one of the large vascular trees

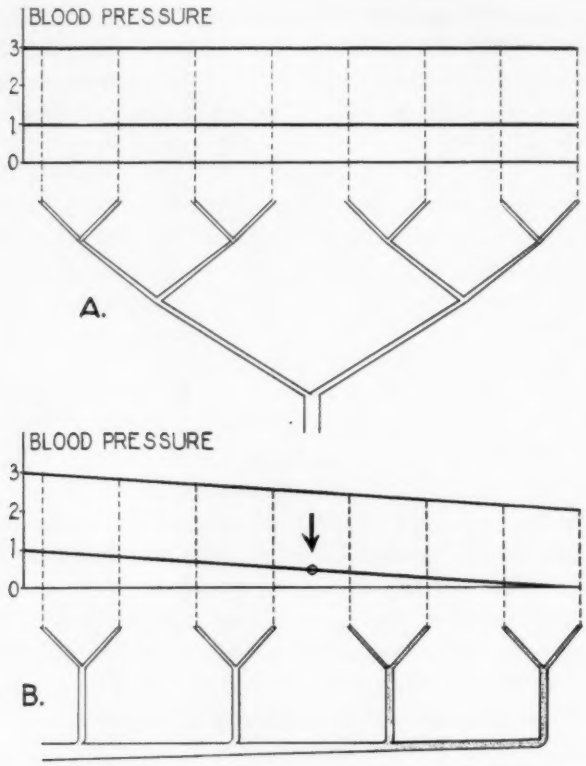

Fig. 11.—Diagram illustrating the effect of a drop in blood pressure on a blood vessel branching dichotomically (*A*) and on a vessel giving off its branches in a rakelike fashion (*B*). In *A* it is assumed that a blood pressure of 3 is normal and that during carbon monoxide poisoning it may drop to 1. There will be blood pressure of 1 on all cross sections of the dichotomically branching vessel. The pressure 1 is supposed to be sufficient to keep the blood flowing at a rate which allows enough exchange of gases for the nerve cells to survive. In *B* the blood pressure of 3 is normally not maintained in all branches of the vessel but falls to 2 along the vessel for hydrodynamic reasons. Pressure 2, however, is supposed to be still more than sufficient for the upkeep of a rapid blood flow. The drop to blood pressure 1 during carbon monoxide poisoning, as in *A*, leaves available sufficient blood pressure only for the two left branches, whereas in the two right branches the pressure, and with it the velocity of blood flow, drops below the critical level (indicated by arrow). These vessels (indicated by stipples) are no more able to supply their nerve cells, which undergo ischemia. The extent to which the fatal drop of blood pressure occurs appears to determine the extent of the resulting lesion. Compare figures 2 and 3.

supplying a certain area in the brain and the conditions will become as difficult for the vessels of this area as for the vascular system of the cornu ammonis, i. e., necrobiosis will also occur in this region. An observation was made on an animal in one hemisphere of the brain of which several such lesions were to be seen (opossum 52, fig. 8). In this case severe poisoning had been produced, and obviously the blood pressure fell to a low level for so long that in some of the arteries the velocity of blood flow decreased in the same way as in the cornu ammonis, i. e., to a degree that the nerve cells no longer received enough oxygen. This case is also interesting in that the one hemisphere suffered much more than the other. An effect such as this can also be explained on the basis of the suggestion outlined here. If the blood pressure is unequal in the two internal carotid arteries, different results of carbon monoxide poisoning may be expected. Whereas in the higher mammals and in man the circle of Willis is probably instrumental in equalizing differences in blood pressure, a possibility of this kind exists only to a minor degree in the opossum, in which the circle of Willis is not closed.[25] Each hemisphere in the opossum is, therefore, more dependent on its respective carotid artery than in the higher mammals, as can be seen in cases of experimental embolism produced with Lycopodium. In the opossum the injection of Lycopodium spores in one carotid artery leads to practically exclusive appearance of ischemic lesions in one hemisphere, whereas after unilateral injection in the dog, which has a closed circle of Willis, lesions are scattered over both hemispheres.[26] Opossum 52 appeared to show that no explanation resorting to special tissue affinities of carbon monoxide or the like can satisfactorily account for the selective effect of carbon monoxide.

Since none of the explanations advanced thus far in respect to the vulnerability of the cornu ammonis in man can be adopted for the opossum, and the evidence for the validity of these explanations in the case of the human brain is admitted by most workers to be meager, the reverse procedure might be tried; i. e., an adaptation of the explanation given for the opossum might be attempted for man.

COMMENT

It has been pointed out how complex appears to be the problem of the vulnerability of the cornu ammonis in man. The question arises whether the simple explanation given for changes in the cornu ammonis of the

25. Voris, H. C.: The Arterial Supply of the Brain and Spinal Cord of the Virginian Opossum (Didelphis Virginiana), J. Comp. Neurol. **44**:403-423, 1927.

26. Bodechtel, G., and Müller, G.: Die geweblichen Veränderungen bei der experimentellen Gehirnembolie, Ztschr. f. d. ges. Neurol. u. Psychiat. **124**:764-793, 1930.

opossum might not be of use in respect to the problem in man. Against this suggestion the objection might be raised that as the opossum is one of the most primitive marsupials and differs from all the Placentalia thus far studied, it is not justifiable, on the basis of results obtained with this animal, to draw conclusions that would be of value in the elucidation of the problem in man. However, this objection seems unsupported by the known facts. Of the physiologic factors that could be so different as to render any conclusion meaningless, the respiratory function of the blood is of primary importance in connection with the problem under investigation. However, Scott [27] reported that the oxygen and carbon dioxide dissociation curves of the opossum closely resemble those of modern Placentalia. Anatomically, it has been observed that the cerebral vascularization of the opossum displays the same angioarchitectonics on the basis of its end arterial pattern as that of other mammals having network systems.[19a] This applies also to the cornu ammonis, in so far as the relative density of capillaries in the cornu ammonis corresponds to that seen in the brains of other mammals. Finally, in regard to the histopathologic reactions observed in cases of gas poisoning, no essential difference exists between the lesions seen in the opossum and those described by various observers in other mammals and in man.[28] It is therefore permissible to make use of the information gained by a study of the opossum in reconsidering the problem of the vulnerability of the cornu ammonis in man.

It has been stated that all propositions made to explain the selective vulnerability of the cornu ammonis when tried on the opossum have proved unsatisfactory, as they have failed thus far to elucidate the problem in man. It is therefore suggested that the theory advanced here for the opossum brain might apply to the human. The two factors discussed in respect to the opossum are found also in man: (1) The blood pressure drops under the influence of carbon monoxide,[29] and (2) the septal vessels of the cornu ammonis in both man and the opposum branch from the hippocampal artery in a rakelike pattern.[30]

The suggestion is made, therefore, that the selective vulnerability of Sommer's sector of the cornu ammonis in man is attributable to a selec-

27. Scott, W. J.: Gas Transport by the Blood of the Opossum, Didelphys Virginiana, J. Cell. & Comp. Physiol. **12**:391-401, 1938.

28. Ferraro, A., and Morrison, L. R.: Illuminating Gas Poisoning, Psychiatric Quart. **2**:506-541, 1928. Hiller.[1d] Meyer.[16]

29. Haldane, J.: The Action of Carbonic Oxide on Man, J. Physiol. **18**:430-469, 1895. Footnote 21.

30. Altschul.[5] The order of magnitude of the vessels supplying Sommer's sector has been correlated with the local vulnerability by L. Alexander and T. J. Putnam (Pathological Alterations of Cerebral Vascular Patterns, A. Research Nerv. & Ment. Dis., Proc. [1937] **18**:471-543, 1938) on page 473 of their paper.

tive drop in the blood pressure in a number of the vessels supplying that sector, in consequence of the same hydrodynamic principle that operated in case of the opossum. This suggestion is supported by the fact that pathologic changes have been observed in the human cornu ammonis in a number of different disturbances, which have in common, however, the same effect on the blood pressure. Thus lesions have been observed in the cornu ammonis, not only in cases of circulatory insufficiency [1] but also in cases of morphinism,[1p] in which abnormally low blood pressures have been recorded,[31] and in cases of infectious diseases of various kinds,[32] which also are accompanied by decrease in blood pressure.[31]

It remains to be seen whether this suggestion, if valid, is to be restricted to the cornu ammonis or whether there has been opened an avenue of approach to the problem of selective vulnerability in the brain in general, which might be useful in dealing with such questions as the vulnerability of the pallidum and the Purkinje cells. It is emphasized, however, that in this paper data are given concerning only the cornu ammonis in the brain of the opossum and that a tentative explanation has been attempted in regard to the opossum exclusively.

SUMMARY

Carbon monoxide poisoning in the opossum affects primarily the cornu ammonis. Only extensive and repeated poisoning with illuminating gas of high carbon monoxide content leads to lesions in other parts of the brain. However, the destruction of the cornu ammonis in such cases is much more serious and occurs long before lesions in other parts of the brain are produced. The pathologic changes occur on a purely vascular basis.

The vulnerability of the cornu ammonis in the opossum is explained by a simple hydrodynamic effect of the drop in blood pressure and the dilatation of the blood vessels on the velocity of blood flow under the influence of carbon monoxide. Whereas in blood vessels branching dichotomically the fall in the blood pressure is distributed equally, in the rakelike pattern of the vascular system of the cornu ammonis the blood

31. Kauffmann, F.: Pathologie des arteriellen Blutdruckes, in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1927, vol. 7, sect. 2, pt. 2, pp. 1407-1413.

32. King, L. S.: Studies on Eastern Equine Encephalomyelitis: I: Histopathology of the Nervous System in the Guine Pig, J. Exper. Med. **68**:677-692, 1938. In plate 34, fig. 9, of this paper bilaterally symmetric necrosis of the pyramidal cells of the cornu ammonis is shown, which is probably not directly connected with the infection, since it is not inflammatory, but may be due to ischemia caused in the way previously suggested. See also footnote 1.

pressure can drop locally below a critical level before this condition occurs in the rest of the brain. On account of the sluggish flow of blood, the nerve cells in these areas are exposed to lack of oxygen and to the poisonous effect of carbon monoxide longer and more severely than are those in areas in which the circulation has not yet reached so low a point.

The suggestion is made that the results obtained in the opossum may lend themselves to a satisfactory explanation of the selective vulnerability of Sommer's sector of the cornu ammonis in man, which has a rakelike vascular pattern of the type seen in the opossum.

CONSTITUTIONAL DIFFERENCES BETWEEN DETERIORATED AND NONDETERIORATED PATIENTS WITH EPILEPSY

IV. THE HANDWRITING

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Previous studies have convinced us that the disorder known as idiopathic epilepsy is grossly divisible into two forms. In the one form mental deterioration occurs, and in the other it does not. The symptoms of epileptic deterioration are too well known to be repeated here; suffice it to say that its presence usually condemns the possessor to institutional care, sometimes for life. In contrast to this, most of the nondeteriorated epileptic patients are not institutionalized, because they become adjusted in the extramural world on a level comparable with that of their nonepileptic fellows. Since the nondeteriorated patients with epilepsy are seldom institutionalized, they have eluded the observation of the classic epileptologists, who were for the most part physicians in institutions. Consequently, there is a paucity of literature on the nondeteriorated epileptic patient, and the literature is especially meager in the discussion of differences between the psychotic and the nonpsychotic person with epilepsy.

For several years we have been engaged in studying certain differences between nondeteriorated and deteriorated epileptic persons, including the constitutional differences. In a previous communication [1] we reported that the deteriorated patients showed a greater profusion of congenital anatomic anomalies (stigmas of degeneracy) than those without deterioration. In another communication [2] we recorded significant differences in body habitus in the two groups, as determined by

From the Department of Nervous and Mental Diseases, Northwestern University Medical School, and the Minnie Frances Kleman Memorial Fund.

1. Paskind, H. A., and Brown, M.: Constitutional Differences Between Deteriorated and Nondeteriorated Patients with Epilepsy: I. Stigmas of Degeneracy, Arch. Neurol. & Psychiat. **36**:1037 (Nov.) 1936.

2. Paskind, H. A., and Brown, M.: Constitutional Differences Between Deteriorated and Non-Deteriorated Patients with Epilepsy: II. Anthropometric Measurements, Am. J. Psychiat. **95**:901, 1939.

anthropometric measurements. In a third communication [3] we described significant differences in the dactylographic patterns (finger prints) in the two groups of epileptic patients. The present study is concerned with another constitutional mark, the handwriting, and represents an attempt to determine whether constitutional differences between deteriorated and nondeteriorated patients are reflected in the handwriting.

There are indications in the literature that handwriting represents a constitutional mark. Thus, Preyer,[4] Flatow-Worms,[5] Poppée,[6] Hirt,[7] Diel,[8] Ufer,[9] Julliot,[10] Kuhlman [11] and Schneidemühl [12] expressed agreement that the essential character of handwrting remains unchanged after the juvenile period. Preyer [4a] also reported the interesting observation that writing retains its individual mark regardless of whether the writing is done with the hand, mouth, head, foot, elbow or knee. Carmena [13] has shown that there is a greater similarity between the handwriting of identical twins than between that of nonidentical twins. Kramer and Lauterbach [14] found that the handwriting of a set of twins of the same sex bears closer resemblance than does that of a set of twins of different sexes. From considerations such as these, it seems reasonable to us that handwriting may be accepted as a constitutional mark and that significant differences in the character of the handwriting may betray differences in the constitutional makeup. It was thought worth while to study the handwriting of deteriorated and of non-

3. Paskind, H. A., and Brown, M.: Constitutional Differences Between Deteriorated and Non-Deteriorated Patients with Epilepsy: III. Dactylographic Studies, to be published.

4. Preyer, W.: (*a*) Zur Psychologie des Schreibens, Hamburg, Leopold Voss, 1895; (*b*) Die Individualität in der Handschrift, in Verhandlungen des internationalen psychologischen Kongress, 1896, Munich, J. F. Lehman, 1896.

5. Flatow-Worms, E.: Handschrift und Charakter, in Die Biologie der Person, Berlin, Urban & Schwarzenberg, 1931, vol. 2, p. 695.

6. Poppée, D.: Graphologie médicale, J. de neurol. **8**:172, 1903.

7. Hirt, E.: Untersuchungen über das Schreiben und Schrift, Psychol. Arb. **6**:551, 1914.

8. Diel, A.: Ueber die Eigenschaften der Schrift bei Gesunden, Psychol. Arb. **3**:1, 1901.

9. Ufer, C.: Schrift und Individualität bei Schulkindern, in Rein, W.: Enzyklopedischer Handbuch der Pädagogik, Langensalza, Germany, H. Beyer & Söhne, 1899, vol. 6, p. 202.

10. Julliot, C. L.: La graphologie et la médecine: IV. Bases fundamentales de la graphologie, Presse méd. **39**:939, 1931.

11. Kuhlman, F.: Zur Psychologie der Schrift des Kindes, Ztschr. f. pädagog. Psychol. **2**:488, 1914.

12. Schneidemühl, G.: Die Psychologie der Handschrift, Neurol. Centralbl. **31**: 224, 1912.

13. Carmena, M.: Schreibdruck bei Zwillingen, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:19, 1935.

14. Kramer, E., and Lauterbach, C. E.: Resemblances in the Handwriting of Twins and Siblings, J. Educ. Research **18**:149, 1928.

deteriorated patients with epilepsy to determine whether differences in constitutional makeup would be reflected in differences in their handwriting. This report is concerned with the results of that study.

MATERIAL AND METHODS

The materials used in the present study consisted of specimens of handwriting of 71 deteriorated patients with epilepsy from the Elgin, Dixon and Chicago State Hospitals and of 40 epileptic patients without deterioration seen in the outpatient clinics of Northwestern University Medical School and Rush Medical College. All the subjects were males. Patients with oligophrenia were not accepted for this study; this disorder was ruled out either by psychometric tests or by the finding of an educational and vocational history incompatible with defective mental development (feeblemindedness). In order to allow time for deterioration to occur, no patient was accepted for the group not showing deterioration unless seizures had been present for at least four years; many of the patients had had seizures for decades. No patient was accepted who showed signs of focal neurologic disorder.

Specimens consisted of the sentence "Careless drivers' disregard for human life is not deliberate, but its tragic results are just as permanent." All specimens were written with the same pen, on an unlined card, 3 by 5 inches (7.6 by 12.7 cm.) in size, with all patients in practically the same position. Each specimen was analyzed for height of small letters (a, r, e, s, i, v, o, u, m, n and c), height of tall letters (l, d, g, f, h, b, t, j and p), width of letters (in the word "deliberate") and ratio of height of small letters to height of tall letters.

RESULTS AND COMMENT

A study of the handwriting of patients with epilepsy reveals interesting differences between that of persons who were deteriorated and that of persons who were not deteriorated. The handwriting of the former group may be seen to be distinctly larger than that of the latter group (figs. 1 and 2 and table 1). This is particularly true of the height of the small letters, which have an average height in the deteriorated group of 3.2 mm. and in the nondeteriorated group of 2.7 mm. The difference of 0.5 mm. in the height of the small letters may be considered statistically significant, since the ratio of the difference to its standard error is 4.42.[15] Similarly, there is a statistically significant difference (with a critical ratio of 4.30) between the height of tall letters in the two groups of patients, the mean height of the tall letters in the handwriting of the deteriorated epileptic patients being 8.0 mm. and that of the nondeteriorated epileptic patients being 6.9 mm. No sig-

15. In accordance with the opinion of Fischer (Fischer, R. A.: Statistical Methods for Research Workers, London, Oliver & Boyd, 1928, p. 45), a difference between two means may be regarded as statistically significant if the ratio of that difference to its standard error is more than 2.0. A ratio of 2.0 indicates that a similar difference is to be anticipated in 95.4 per cent of repetitions of a similar experiment.

nificant difference is found in the width of letters written by the two groups of patients. The mean for this value is 4.2 mm. for the deteriorated patients and 3.9 mm. for the nondeteriorated ones. The ratio of the height of small letters to the height of tall letters also shows a significant difference between the two groups of epileptic patients. This ratio is 0.409 in the handwriting of deteriorated epileptic patients and 0.362 in the handwriting of nondeteriorated epileptic patients. The critical ratio for the difference between these two measurements is 3.33.

Fig. 1.—Specimens of handwriting from 71 epileptic patients with deterioration.

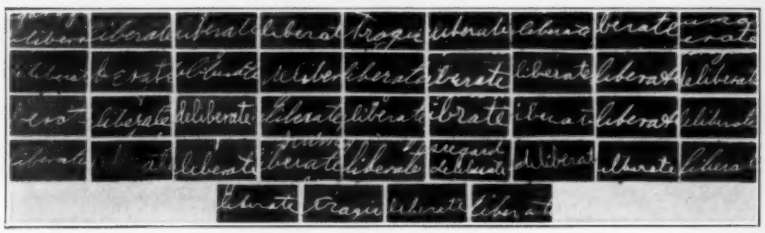

Fig. 2.—Specimens of handwriting from 40 nondeteriorated epileptic patients.

It thus appears that the height of small letters and of tall letters is greater in the handwriting of deteriorated epileptic patients than in that of nondeteriorated ones and that these differences when treated statistically are found to be significant. It seems reasonable to believe that deteriorated persons with epilepsy write with larger characters than do the nondeteriorated patients. Similarly, the ratio of the height of small to that of tall letters is greater for the deteriorated patients, and this difference is statistically significant.

The presence of larger handwriting in a group of deteriorated patients as compared with the handwriting in a group of nondeteriorated patients

to an extent and consistency at which such differences are statistically significant requires explanation. The point suggests itself that since children or, in other words, persons who have not yet attained a complete degree of cerebral maturity, write with large characters, it is possible that the large handwriting of deteriorated epileptic persons may be due to arrested, incomplete development of the handwriting mechanism and that the causes of the large handwriting here are the same as the causes producing large handwriting in children. Another possible explanation is that large handwriting may be a product or a symptom of mental deterioration. In that case large handwriting should be found in patients with other forms of mental deterioration, such as dementia.

In order to throw light on this question, we studied as controls specimens of handwriting from two groups of subjects. Those in the first group had not reached an adult level of cerebral development. In this group there were 40 imbeciles, 44 school children in the second and third grades, 46 school children in the fourth and fifth grades and 49 school children in the sixth and seventh grades. We believe that the presence of large handwriting in this group of subjects would lend evidence to support a view that the large handwriting of deteriorated epileptic patients is due to arrested or defective development of the handwriting mechanism. The second control group consisted of 51 deteriorated patients with dementia praecox and 45 demented patients in the advanced stages of dementia paralytica. If large handwriting (to the degree of statistical significance) were to be found in this group of patients it would indicate that the large writing of the epileptic patients is a product of deterioration or dementia, and not a result of arrested or defective development.

TABLE 1.—*Size of Handwriting of Deteriorated and of Nondeteriorated Patients with Epilepsy*

	Deteriorated Patients (71)			Nondeteriorated Patients (40)		
	Mean	Standard Deviation	Standard Error of Mean	Mean	Standard Deviation	Standard Error of Mean
Height of small letters, mm..	3.2	0.756	0.0898	2.7	0.434	0.0685
Height of tall letters, mm....	8.0	1.43	0.170	6.9	1.21	0.192
Width of letters, mm.....	4.2	1.15	0.137	3.9	0.762	0.120
Ratio of small letters to tall letters.....	0.409	0.0916	0.0118	0.362	0.0571	0.00817

Specimens of handwriting were also obtained from 46 men with no nervous or mental disease.

The size of the handwriting in these groups of persons is shown in table 2, and typical specimens of their handwriting appear in figures 3 to 9.

A study of tables 1 and 2 shows interesting data. The mean height of the small letters is significantly greater in the handwriting of deteriorated epileptic patients than in that of patients with either dementia praecox or dementia paralytica (3.2 mm., as compared with 2.6 and 2.9 mm., respectively, with critical ratios of 5.13 and 2.08). Between the height of small letters as found in the handwriting of

nondeteriorated patients, on the one hand, and that as found in the writing of patients with dementia praecox or dementia paralytica, on the other, there are no significant differences (2.7 mm. as compared with 2.6 and 2.9 mm., respectively). In other words, the mean height of small letters in the writing of deteriorated epileptic patients is significantly greater than the corresponding value in the handwriting of nondeteriorated epileptic patients, patients with dementia praecox and patients with dementia paralytica.

The mean height of the tall letters in the handwriting of deteriorated epileptic patients is greater than that of nondeteriorated ones (table 1),

TABLE 2.—*Size of Handwriting in Various Groups of Persons*

	Patients with Dementia Praecox	Patients with Dementia Paralytica	Imbeciles	School Children, Second and Third Grades	School Children, Fourth and Fifth Grades	School Children, Sixth and Seventh Grades	Normal Adults
Number of subjects.....	51	45	40	44	46	49	46
Height of small letters, mm.							
Mean.....	2.6	2.9	3.2	5.3	3.1	2.8	2.5
Standard deviation.....	0.531	0.758	0.750	1.77	0.942	0.579	0.540
Standard error of mean	0.0745	0.113	0.119	0.266	0.139	0.0827	0.0797
Height of tall letters, mm.							
Mean.....	7.4	7.6	7.4	10.1	7.3	7.4	7.4
Standard deviation.....	1.32	1.75	1.59	2.92	1.73	1.63	1.39
Standard error of mean	0.184	0.260	0.251	0.441	0.254	0.232	0.206
Width of letters, mm.							
Mean.....	3.3	4.3	4.3	5.9	4.1	3.7	4.1
Standard deviation.....	0.906	1.14	1.26	1.69	0.980	0.807	0.793
Standard error of mean	0.129	0.170	0.199	0.254	0.144	0.115	0.117
Ratio of small letters to tall letters							
Mean.....	0.358	0.388	0.426	0.515	0.426	0.378	0.347
Standard deviation.....	0.0688	0.0735	0.0799	0.0827	0.0724	0.0486	0.0678
Standard error of mean	0.00965	0.0109	0.0126	0.0125	0.0107	0.00696	0.0100

and also is greater than that of patients with dementia praecox (8.0 mm. as against 7.4 mm., with a critical ratio of 2.39) and of patients with dementia paralytica (8.0 mm., as against 7.6 mm.). Only the first two differences are statistically significant.

The width of the letters in the writing of epileptic patients with deterioration is greater to a significant extent than that of either the nondeteriorated epileptic patients (table 1) or the patients with dementia praecox (4.2 mm., as against 3.3 mm., with a critical ratio of 4.78). It is slightly less (not significantly so) than the width of the letters in the handwriting of patients with dementia paralytica.

The ratio of the height of small letters to that of tall letters is greater in the handwriting of patients with epileptic deterioration than in the handwriting of nondeteriorated epileptic patients and patients with

Fig. 3.—Specimens of handwriting from 51 patients with dementia praecox.

Fig. 4.—Specimens of handwriting from 45 patients with dementia paralytica.

Fig. 5.—Specimens of handwriting from 40 imbeciles.

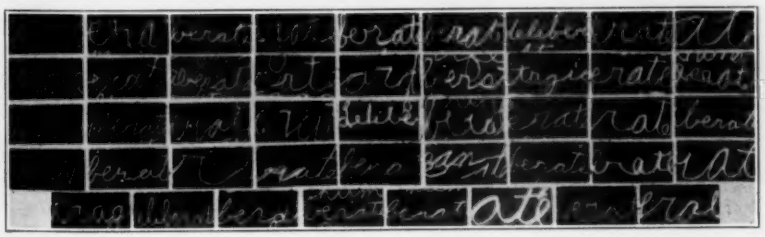

Fig. 6.—Specimens of handwriting from 44 school children in the second and third grades.

dementia praecox or dementia paralytica (0.409, as compared with 0.362, 0.358 and 0.388, respectively, the critical ratios being 3.33, 3.51 and 1.36, respectively). Only the last of these differences is not statistically significant.

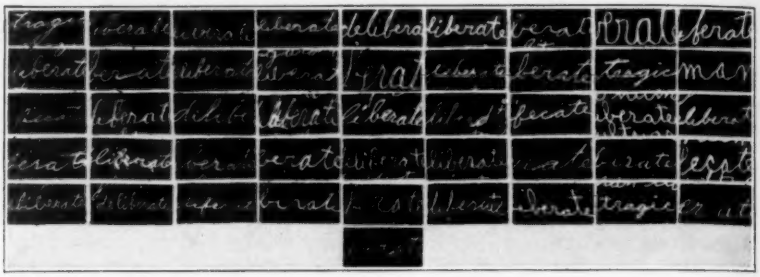

Fig. 7.—Specimens of handwriting from 46 school children in the fourth and fifth grades.

Fig. 8.—Specimens of handwriting from 49 school children in the sixth and seventh grades.

Fig. 9.—Specimens of handwriting from 46 normal adults.

It may be said that with few and unimportant exceptions the same differences in the size or proportions of handwriting are present between deteriorated and nondeteriorated epileptic patients as are present between deteriorated epileptic patients and patients with dementia praecox and dementia paralytica. No significant differences were found between

the handwriting of the extramural epileptic patients and the patients with dementia praecox or dementia paralytica. This suggests that the mental deterioration per se which occurs in institutionalized epileptic patients is not the cause of differences in handwriting which these patients show when compared with the nondeteriorated epileptic patients.

Further study of tables 1 and 2 shows that the specimens of handwriting of deteriorated epileptic patients resemble those of imbeciles and younger children, whereas the writing of the nondeteriorated subjects resembles that of older children and of normal adults. This indicates that in the mentally deteriorated epileptic patients the handwriting mechanism has not reached the normal level of development and is no more completely developed than that of imbeciles or young school children. This is not true of the nondeteriorated epileptic patients. For example, the mean value for the height of the small letters is 3.2 mm. in the handwriting of imbeciles, 5.3 mm. in that of children of the second and third grades, 3.1 mm. in that of children of the fourth and fifth grades and 2.8 mm. in that of children of the sixth and seventh grades. For deteriorated epileptic patients the corresponding value is 3.2 mm., and for nondeteriorated patients it is 2.7 mm. In the handwriting of normal adults the value is 2.5 mm. The findings for the height of the tall letters are not as significant as those just given. However, in comparing the width of letters in the various groups it is again found that the handwriting of institutionalized epileptic patients resembles that of imbeciles and young school children much more than does that of nonpsychotic epileptic patients. The handwriting of the latter, on the other hand, resembles that of older school children and adults. Similar but more striking findings are noted when one examines the mean values for the height of the small letters divided by those for the height of the tall letters. Again, the value for the institutionalized epileptic patients approximates that of imbeciles and young school children, whereas that for the extramural epileptic patients is not significantly different from that for normal adults or older school children.

SUMMARY

A study of the literature reveals evidence that handwriting may be accepted as a constitutional mark. The handwriting of the 71 deteriorated and the 40 nondeteriorated epileptic patients was studied for the size of letters and the ratio of the height of the small letters to that of the tall letters. As controls similar data were obtained from 51 patients with dementia praecox, 45 patients with dementia paralytica, 40 imbeciles, 44 school children in the second and third grades, 46 school children in the fourth and fifth grades, 49 children in the sixth and seventh grades and 46 adults with no nervous or mental disease.

All the subjects were males. The following statistically significant differences were found.

1. The average height of the small letters in the handwriting of deteriorated epileptic patients is significantly greater than in the handwriting of nondeteriorated patients.

2. The handwriting of the institutionalized epileptic patients shows a greater mean value for the height of the tall letters than does the handwriting of extramural epileptic patients.

3. The ratio of the height of the small letters to the height of the tall letters is greater in the handwriting of deteriorated epileptic patients than it is in the specimens of writing obtained from the nondeteriorated patients.

Evidence was presented to show that the foregoing differences are due not to mental deterioration in the institutionalized patients but probably instead to differences in development of the cerebral centers used in writing.

In conclusion, it appears that a constitutional difference in the character of the handwriting is present between mentally deteriorated and nondeteriorated patients with epilepsy. Further, this difference is probably due to a failure of the cerebral centers used in writing to attain full maturity in the deteriorated patients.

Drs. Charles F. Read, Warren G. Murray and Edward F. Dombrowski, managing officers, respectively, of the Elgin State Hospital, Dixon State Hospital and Chicago State Hospital, gave us permission to study patients in these institutions. Dr. Peter Bassoe gave us permission to study patients in the outpatient department of Rush Medical College, University of Chicago. Miss Eleanor G. Nicholson, principal of the Prescott School, granted us permission to obtain specimens of handwriting from school children.

ACTION POTENTIALS OF MUSCLES IN ATHETOSIS AND SYDENHAM'S CHOREA

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In the present report an attempt will be made to analyze the action potentials of muscles during involuntary movements of patients suffering from athetosis, dystonia and chorea. It has been possible to understand certain features of normal motor innervation by a similar analysis already reported.[1] Subsequently, the management of disturbed movement in "spasticity"[2] was studied. Next, "rigidity" with or without tremor, as in Parkinson's disease, and other forms of rigidity and tremor[3] were investigated by the same method.

METHODS AND MATERIAL

The method of recording and the instruments used have been described in detail.[1] Potentials were traced from the surface of whole muscles by suitable flat metal electrodes and from single motor units or small groups of units by coaxial needle electrodes. In a few instances a large Cambridge string galvanometer was used for direct recording. In the majority of cases the potentials were highly amplified and were recorded with a cathode ray oscillograph or, whenever simultaneous tracings were made, with a six channel ink-writing oscillograph.

Records in the last 3 cases in this series were taken with a three channel ink-writing oscillograph constructed by Dr. J. Roy Smith and Mr. C. P. Walter, who also gave us permission to study some of their electroencephalographic records of children suffering from chorea.

Action potentials of 23 patients were thus investigated. Twenty of these had unilateral or bilateral athetosis, and 3 had Sydenham's chorea.

This is the fourth of a series of clinical and experimental studies of motor disorders.

From the Department of Nervous and Mental Diseases, Harvard Medical School, and the Neurological Unit, Boston City Hospital, Boston; and from the Department of Neurology, Columbia University College of Physicians and Surgeons, and the Neurological Institute.

1. Hoefer, P. F. A., and Putnam, T. J.: Action Potentials of Muscles in Normal Subjects, Arch. Neurol. & Psychiat. **42**:201 (Aug.) 1939.

2. Hoefer, P. F. A., and Putnam, T. J.: Action Potentials of Muscles in "Spastic Conditions," Arch. Neurol. & Psychiat. **43**:1 (Jan.) 1940.

3. Hoefer, P. F. A., and Putnam, T. J.: Action Potentials of Muscles in Rigidity and Tremor, Arch. Neurol. & Psychiat. **43**:704 (April) 1940.

RESULTS

The analysis of motor action potentials in this report is essentially limited to the spontaneous involuntary impulses pathognomonic of the two diseases. Voluntary and passive movement and reflexes have been studied as in previous investigations. However, the constant presence of the involuntary impulses, especially while the patients are being examined, makes it virtually impossible to recognize clearly the other types of movement and to distinguish their electromyographic patterns in the flood of impulses set up by each contraction. This is true both for patients who have retained voluntary movement to some extent and for those in whom spasticity and paralysis of varying degrees are superimposed on the athetosis. The physiologic significance of the coexistence, on the one hand, of spasticity and athetosis and, on the other, of alternating tremor and both athetosis and chorea will be discussed later.

Herz [4] made a careful analysis of the pathologic movements by means of motion pictures, which revealed a number of features not well understood before. Wilson [5] recognized the peculiar character of the movements as simultaneous irregular innervations of the protagonists and the antagonists. The electromyographic pattern of the movements has been described as resembling the normal by several earlier investigators.[6]

This could be confirmed to a certain extent by our own records. In figure 1 a number of observations from different patients are shown. The tracings were obtained with the cathode ray oscillograph in leads from whole muscles and from motor units, respectively. The first two records (*A* and *B*) were taken with surface electrodes from the forearm musculature of 2 patients. They show frequencies and amplitudes quite similar to those of normal persons during voluntary effort of moderate strength. There is at times a certain unevenness in the height and number of spikes, but in other parts of the same records both may be perfectly constant. The following four records (*C* to *F*) were taken with coaxial pairs of needle electrodes. The first two of these (*C* and *D*) were from the same patient from whom record *B* was taken with a surface lead. The other two were from the trapezius muscle and from an extensor muscle of the forearm, respectively, of 2 other patients. All four motor unit records show the irregular pattern seen during normal

4. Herz, E.: Die amyostatischen Unruheerscheinungen, J. f. Psychol. u. Neurol. **43**:3, 1931.

5. Wilson, S. A. K.: Modern Problems in Neurology, New York, William Wood & Company, 1929.

6. (*a*) Fahrenkamp, K.: Ueber einen atypischen Fall von Chorea minor mit Laehmungserscheinungen, nebst einem Beitrag zur Kenntnis des Gordon'schen Reflexes, Deutsche Ztschr. f. Nervenh. **54**:324, 1916. (*b*) Cobb, S.: An Electromyographic Study of Chorea, Bull. Johns Hopkins Hosp. **30**:35, 1919.

voluntary effort of low or moderate intensity.[1] By comparison of the records from the surface leads with those from motor units it is seen that a uniform pattern is not forced on the motor unit management in this condition, while in spasticity [2] and rigidity [3] such is the case. The last two records (*G* and *H*), from surface leads, show choreic bursts of impulses from the tongue. Here the unevenness is possibly a little more marked than in records from the other surface leads.

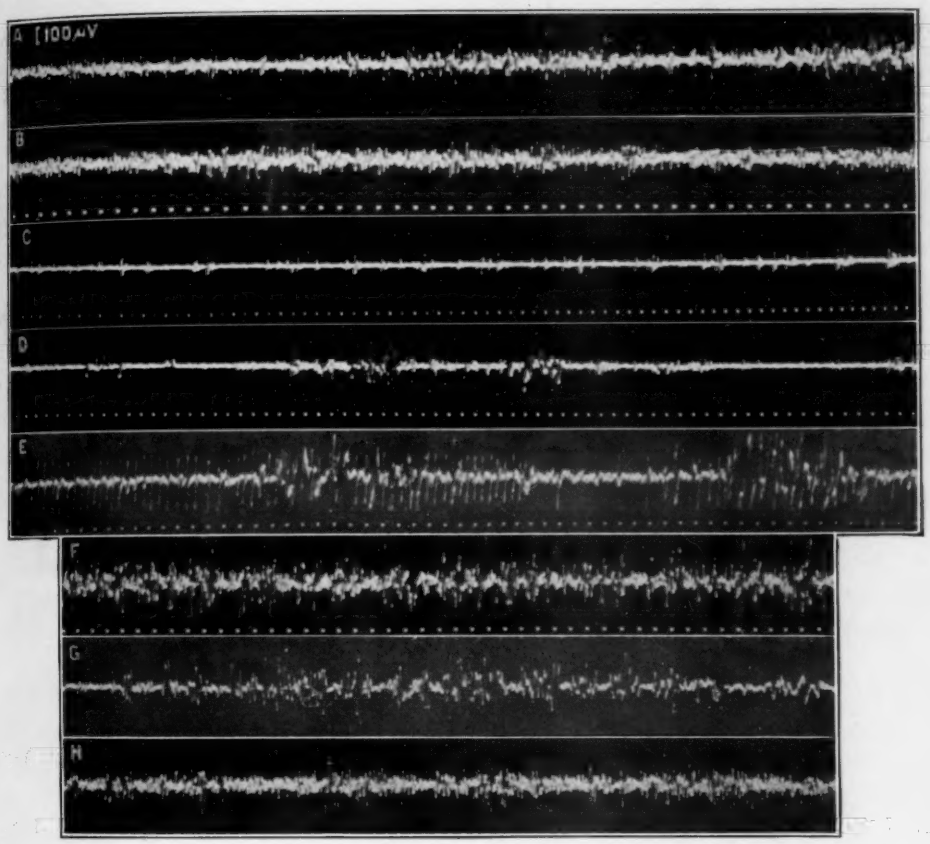

Fig. 1.—Involuntary movement in athetosis and chorea. Cathode ray oscillograph. Time: one-sixtieth second between flashes. Calibration: 3.3 mm. per one-hundredth microvolts on first record. *A* (patient J. F., with athetosis), surface lead on the musculature of the forearm; *B* (patient P. G., with athetosis), surface lead on the musculature of the forearm; *C* and *D* (patient P. G., with athetosis), successive records from coaxial leads from the same muscle as that used in *B*. Note irregular spikes from single units (*C*) and presumably small groups of units (*D*). *E* (patient E. S., with athetosis), coaxial needle leads from the trapezius muscle; *F* (patient B. A., with athetosis), coaxial needle leads from the extensor muscle of the forearm and *G* and *H* (patient T. K., with chorea), surface leads from the tongue.

In figure 2 the relation of a pair of antagonist muscles is shown in two records taken from surface leads. It is seen that both muscles are activated simultaneously most of the time and that their activities are independent of each other. There is no "reciprocal innervation" or inhibition of one group while the antagonist group is active. Furthermore, the type of activity in one group is not influenced by the activity in the other; while one group is under a "tetanic" innervation the activity of the other group may consist in repeated jerks at a slow or fast rate, or may even cease completely. It is thus safe to conclude that no reflex innervation of one group of muscles is brought about by a stretch produced by its antagonists. Another characteristic of athetoid movement

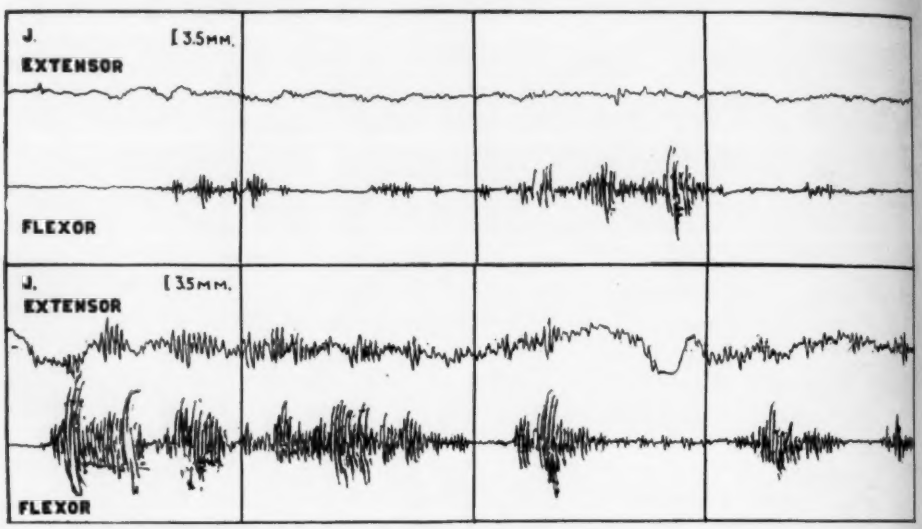

Fig. 2 (patient B. J.).—Involuntary movement in a patient with athetosis when at "rest." Simultaneous records of extensor and flexor groups of the forearm from surface leads. Ink-writing oscillograph. Time: One second between vertical lines. Calibration: 3.5 mm. per one hundred microvolts. Note simultaneous irregular innervation of antagonists.

is revealed by observation of action potential patterns extended over a longer period, namely, that there are periods of rest in one or both groups of muscles during which no electric activity is observable. This seems to indicate that, unlike the situation in parkinsonian or decerebrate rigidity, there is no basic or "tonic" innervation in athetosis.

The relation of two pairs of motor units of antagonist muscles to each other is seen in figure 3. Complete independence of units of a muscle and, again, simultaneous innervation of opposing muscle groups of irregular nature are brought out more clearly by this technic. The

relation of units of one muscle is often indistinguishable from that found in the normal muscle, and only the irregular simultaneous innervation of antagonists characterizes the diseased state.

In figure 4 three records of simultaneous leads from muscles of a patient with chorea are presented. The first shows simultaneous tracings from two motor units of an extensor muscle of the forearm. Here, again, the asynchronous polyrhythmic management of the normal muscle is

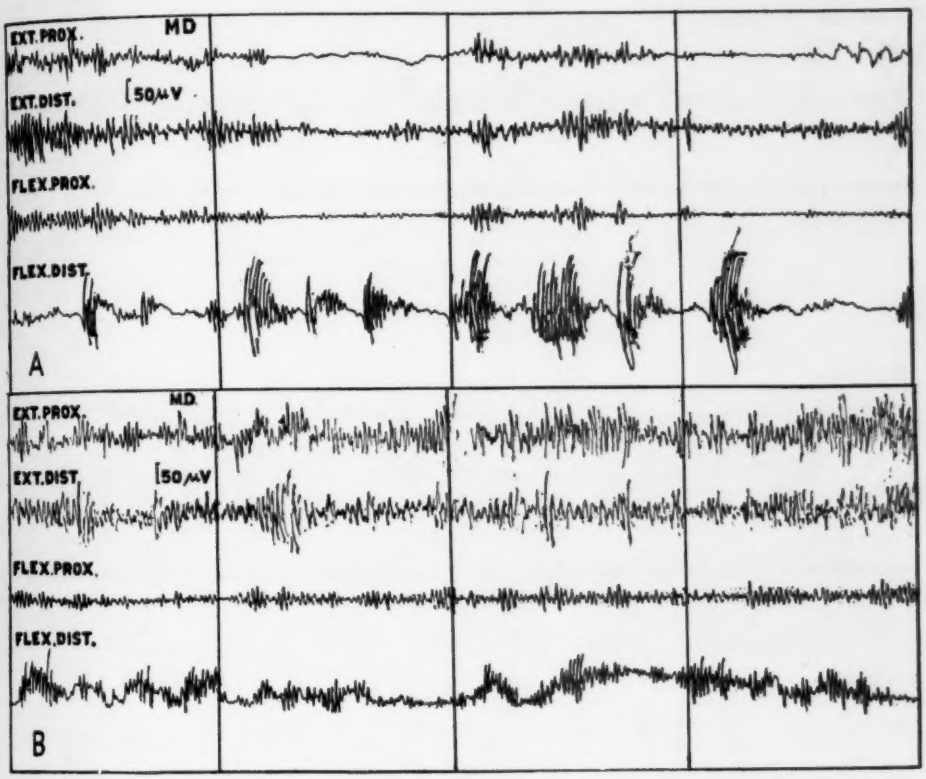

Fig. 3 (patient M. D.).—Involuntary movement in a patient with athetosis. Simultaneous records of two motor units (or small groups) each of extensor and flexor muscles (antagonists) during "rest." Ink-writing oscillograph. Time: one second between vertical lines. Calibration: 50 microvolts. Note complete independence of units of one muscle and simultaneous irregular innervation of antagonists.

recognizable, as well as the similarity in pattern of choreatic and athetoid movement. The second record illustrates this even more clearly. Here, two simultaneous tracings of extensor and flexor muscles from surface leads show the simultaneous irregular activity exactly as in athetosis. The third record shows activity in the flexor muscle alone, while the

extensor is at complete rest. It should be noted that amplitudes of the potentials in chorea are consistently lower than those in athetosis.

It has been mentioned before that both athetoid and choreatic movements may coexist with alternating tremor of the parkinsonian type and with other rhythmic involuntary movements. Instances of this

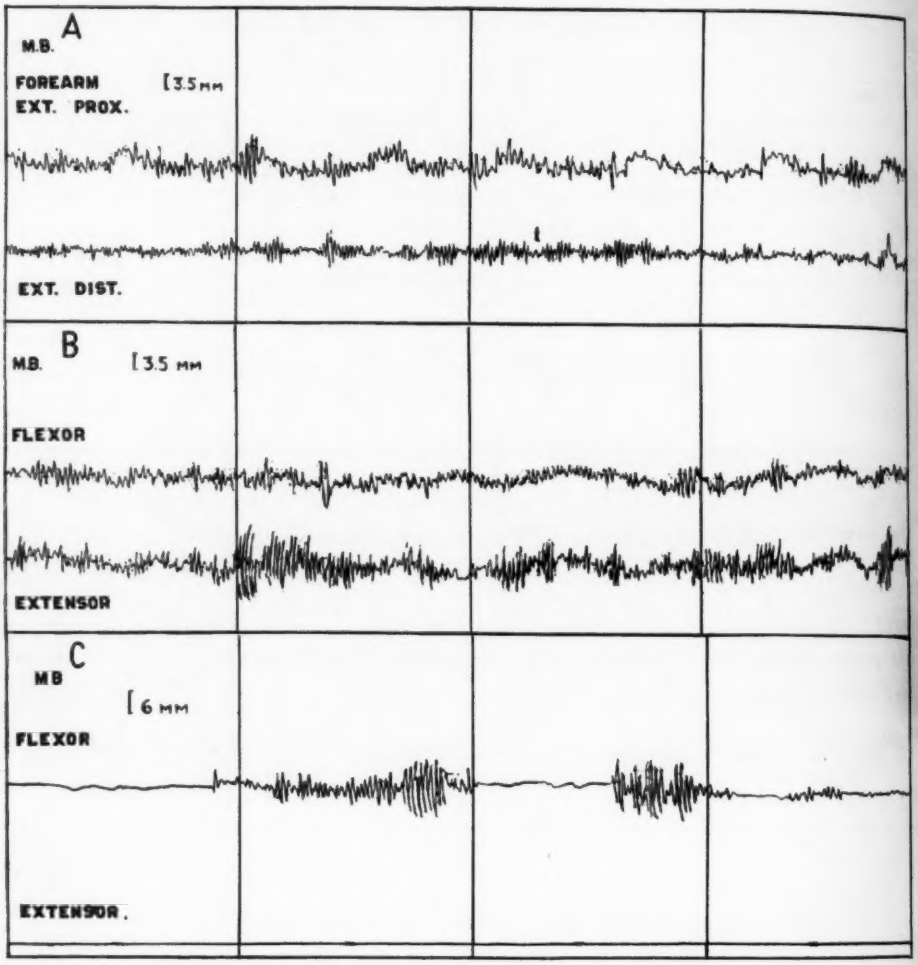

Fig. 4 (patient M. B.).—Involuntary movement in a patient with chorea when "at rest." Simultaneous records of (*A*) two motor units of an extensor muscle of the forearm from coaxial needle leads, and (*B*) and (*C*), from flexor and extensor muscles from surface leads. Ink-writing oscillograph. Time: one second between vertical lines. Calibration: 3.5 and 6.0 mm. for 50 microvolts, respectively. Note similiarity of management of motor unit and antagonists in chorea and in athetosis.

combination are shown in figure 5. The first record is a simultaneous tracing from an extensor muscle of the forearm showing alternating tremor and from the trapezius muscle on the same side in an athetotic movement, both taken with surface leads. The patient had athetosis and, in addition, a slight parkinsonian tremor of one arm and both legs. The second record is another surface run showing alternating tremor in a patient who had repeated attacks of Sydenham's chorea. The last record, also from surface leads, is from a patient with rhythmic torticollis who otherwise presented a dystonic form of athetosis.

A "spastic" component may be present in athetosis. In figure 6 are shown records obtained from a patient who, after "birth injury,"

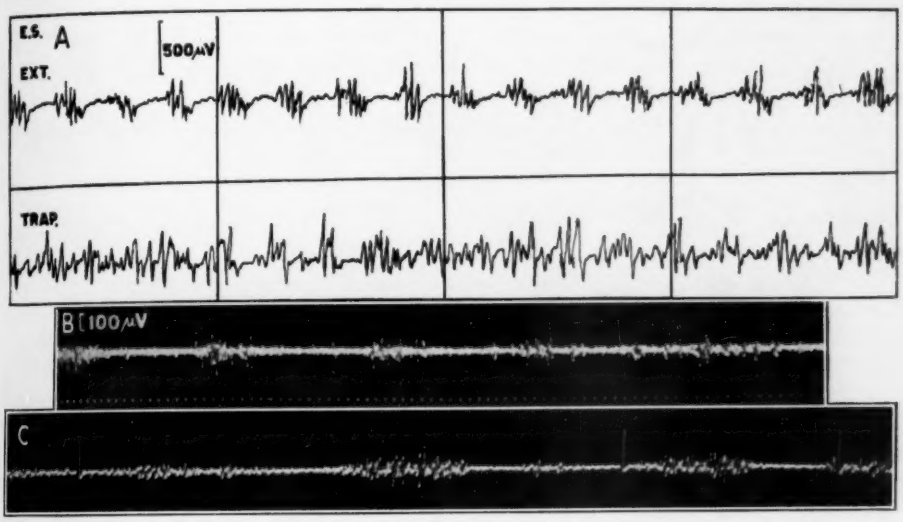

Fig. 5.—Alternating tremor and other rhythmic manifestations in a patient with athetosis and chorea. *A* (patient E. S., with athetosis combined with tremor), simultaneous records of tremor of the forearm and squirming athetoid movements in the ipsilateral trapezius muscle, both from surface leads. Ink-writing oscillograph of Dr. Smith and Mr. Walter. Time: one second between vertical lines. Calibration: Deflection for 500 microvolts marked on record. *B* (patient T. K., with chorea), tremor of the forearm in surface leads. Cathode ray oscillograph. Time: one-sixtieth second between flashes. Calibration: 3.3 mm. per hundred microvolts. *C* (patient M. D., with athetosis), record of rhythmic torticollis from the sternocleidomastoid muscle; surface leads. Cathode ray oscillograph. Time: one-sixtieth second between flashes. Calibration: 3.3 mm. per hundred microvolts.

presented paraplegia combined with athetosis. Among other clinical features of spasticity as defined elsewhere,[2] she showed weakness and increased deep reflexes, with a tendency to clonus. This was confirmed physiologically by a tendency to synchronous motor unit discharge in certain muscles, while others, presenting an athetoid rather than a spastic

condition, showed the asynchronous type of motor unit management already described. This synchronization, though never as marked as in pure spasticity, was nevertheless noticeable both during voluntary and involuntary movements.

The pattern of voluntary movement in cases of pure athetosis is not essentially different from that of involuntary movement. This is easily understood from the previous descriptions. Voluntary movement, how-

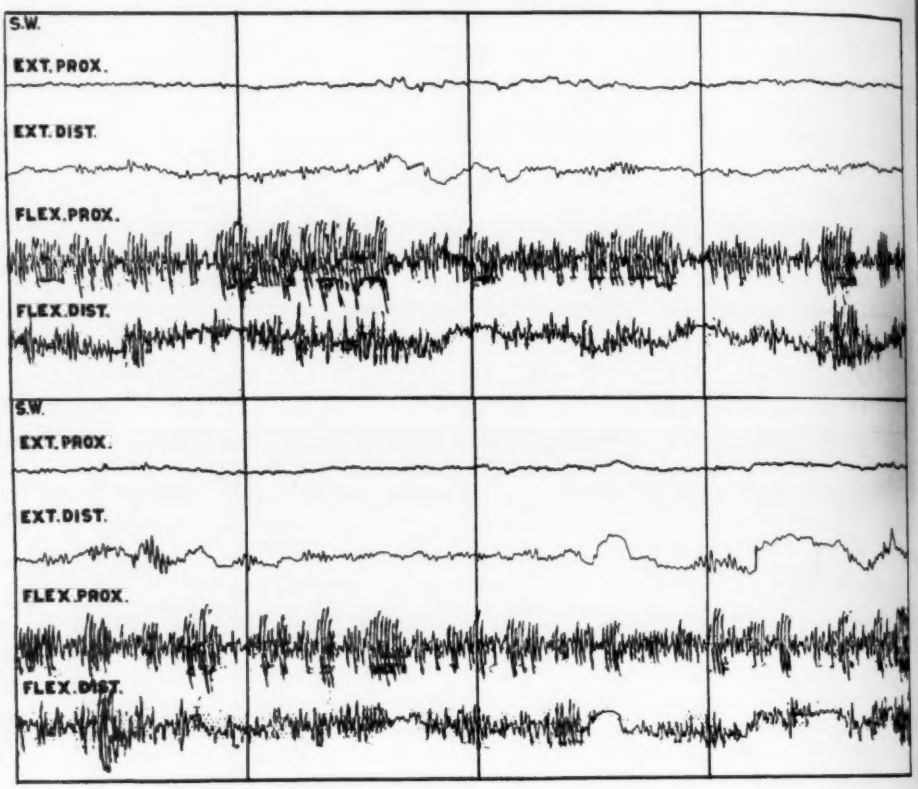

Fig. 6 (patient S. W.).—Combination of "spasticity" and athetosis. Simultaneous records of two motor units each from two antagonist muscles at rest. Ink-writing oscillograph. Time: one second between vertical lines. Calibration: 50 microvolts marked. Note tendency to synchronization of units of the same muscle.

ever, is apparently much harder for the patient to regulate and is usually more powerful in athetosis than in normal states in the performance of the same act. This overshooting in intensity might be explained by the assumption that involuntary as well as voluntary impulses reach the muscle and cannot be differentiated with our method of recording. One

intelligent patient stated that whenever he intended a certain movement the opposite one would occur; it is possible that in order to overcome this faulty direction of effort more strength is used by the patient. The pattern of action potentials during voluntary movement in patients with athetosis is usually one of high frequency and amplitude of spikes, with both features near or even beyond the upper normal limit. Spike frequencies of 450 per second are not unusual. It seems likely that higher frequencies occur, but they could not be clearly recognized with the technic of recording available.

Proprioceptive reflexes could be elicited clearly in a number of cases. They were usually more complex in structure than is normal and resembled what was considered [2] the spastic type of response, consisting of a number of spikes with after-discharges. Records of biceps and ankle jerks are shown in figure 7. It was not possible to study reflexes spreading to other levels, as in cases of spasticity. The unpredictable

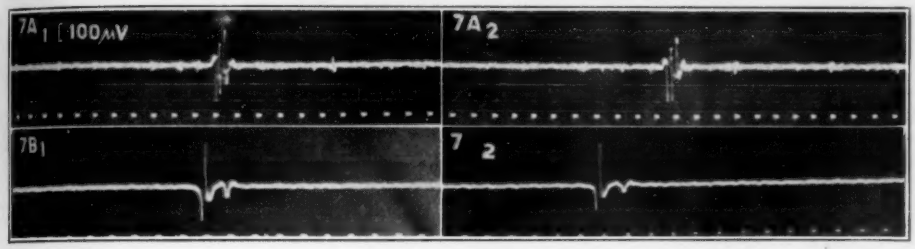

Fig. 7.—Reflexes in athetosis; surface leads. Cathode ray oscillograph. Time: one-sixtieth second between flashes. Calibration: 3.3 mm. per 100 microvolts on first record. *A* (patient P. G.), biceps reflex responses. Note repetition of spikes and "background" activity in the muscle. *B* (patient L. S.), ankle jerk responses. Note comparatively simple character of spikes.

involuntary movements everywhere made it impossible to trace small groups of "escaped" impulses of low amplitude.

COMMENT

The action potentials of muscles during involuntary movements in patients with athetosis and Sydenham's chorea were the chief subject of this study. In cases of the uncomplicated form, i. e., in the absence of spasticity or tremor, the patterns thus recorded in the two diseases resemble each other and at the same time show great similarity to those of normal muscles during voluntary contraction. This normal appearance, at least in a number of respects, was first noted by Fahrenkamp [6a] and by Cobb [6b] in cases of Sydenham's chorea. Lindsley [7] saw action

7. Lindsley, D. B.: Electromyographic Studies of Neuromuscular Disorders, Arch. Neurol. & Psychiat. **36**:128 (July) 1936.

potentials which resembled those of normal movement in some of his cases of athetosis. It was noticed by all observers, however, that the sequence of potentials was irregular and often unsustained and in that respect was different from the normal. In the clinical literature a sharp distinction was made between the seemingly simple choreatic movements, sometimes described as "normal," and the bizarre, complicated distortions of athetosis, of which it is difficult to give an adequate description.[8] Oppenheim [9] first mentioned that in cases of athetosis palpation of antagonist muscles showed them to be simultaneously under tension. A clear concept of the nature of these movements, however, was not reached until Wilson,[5] by means of mechanical myograms, recognized that in both disorders simultaneous innervation of antagonist muscles occurs constantly and irregularly, an "abrogation of the law of reciprocal innervation." Herz's analysis of slow motion pictures [4] of patients with athetosis and with chorea has widely confirmed Wilson's [5] statement that "resemblances are more impressive than differences" in the physiologic state underlying the motor disorders in the two conditions. He demonstrated, among other facts not accessible to direct clinical observation, that the supposed difference between the quick movements in chorea and the long-sustained movements in athetosis is more apparent than real. Thus, in some instances long-sustained movements of bizarre nature are the result of quick jerks blended into one motion by the eye but clearly separable by the camera.

Lewy [10] concluded from his records of movements in cases of chorea that as the movements are sometimes "normal" and sometimes abnormal, chorea cannot be a clinical entity. The experimental evidence of this investigation tends to show that no matter how movements appear in cases of Sydenham's chorea and of athetosis, similar mechanisms are active, as far as management of motor units and of antagonists is concerned, and that differences in the motion produced are more those of degree than of character. Nevertheless, it is not unlikely that the choreas, athetoses and dystonias should be redefined and regrouped in the future.

Other questions raised by this discussion are: What constitutes "normal" movement, and what is its relation to "voluntary" movement?

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8. Spatz (Spatz, H.: Physiologie und Pathologie der Stammganglien, in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1927, vol. 10, p. 318), for example, compared the quick movement in chorea with the normal galvanic reaction and the slow tetanic movement in athetosis with the wormlike contraction in the reaction of degeneration.

9. Oppenheim, H.: Lehrbuch der Nervenkrankheiten, ed. 5, Berlin, S. Karger, 1908.

10. Lewy, F. H.: Die Lehre vom Tonus und der Bewegung, Berlin, Julius Springer, 1923.

It has been pointed out repeatedly in this report that the similarity in appearance of voluntary movement of normal subjects and that of involuntary movement of patients with athetosis and chorea is borne out by the fact that in all instances motor units act independently and asynchronously. This was found to be in contrast to another type of motor unit management, namely, the synchronous discharge, which was seen in patients with spastic conditions whose lesions were at least predominantly in the pyramidal tracts and also, with a certain modification, in patients with parkinsonian rigidity and tremor. Synchronization, or a tendency toward it, was found in all movements in these states, including voluntary movement, whenever the patients were able to carry it out. To be sure, voluntary movement in these conditions is less good than normally; nevertheless, it is the result of a volitional act. It seems justifiable to conclude, therefore, that "voluntary" movement may be performed by utilization of at least two different mechanisms. The first is "normal" and is somehow related to the normal function of the pyramidal motor system, and also presumably of all the other motor systems. Fatigue is minimal and the movement smooth and precise. This we assume is due to the inhibition of antagonists and to the fact that motor units take turns under the management of distributor mechanisms. The second mechanism is pathologic and is apparent when (as we assume) intrinsic motor systems of the cord dominate the pattern, though the intrinsic system innervation must be set off by impulses coming from high cerebral levels, possibly utilizing residual fibers or contralateral or aberrant fibers of the pyramidal tracts. The voluntary movements in these conditions are "rigid" or "spastic," i. e., stiff, weak, clumsy and subject to easy fatigue. This was explained by the synchronous stimulation of the available motor units and by activation of the antagonists of the innervated muscles through a stretch reflex mechanism, which could not be inhibited as in normal persons.

In our observations two different types of athetoid movements were seen, one in which asynchronous, independent motor unit discharges of "normal" appearance were recorded and another, present in rare cases, in which spasticity was superimposed when the motor units were synchronized. In both forms, however, antagonists were active simultaneously and irregularly. This has been considered an outstanding feature of these motor disorders.[11]

11. It is obvious that the same set of muscles can act as antagonist in one and as synergist in another movement, both being normal. This form of synergism, as in the "straight left" given as an example by Wilson,[5] is only an apparent contradiction to Sherrington's "law of reciprocal innervation." Clinical observations and electrical studies show that simultaneous activity in antagonist muscles occurs in intended simple movements of patients, such as bending an arm, and it has already been mentioned that an intelligent patient of ours experienced exactly this faulty innervation.

It is too early at this stage to decide whether the two observable types of motor unit management associated with athetosis imply the existence of two different pathways by which the motor impulses reach the place, presumably in the cord, where the motor units for one muscle (originating usually in a number of segments) are sent into action.

It is interesting to note in this connection that Wilson,[5] in his discussion of the pathogenesis of choreoathetosis, expressed the belief that these motor disorders are mediated by the pyramidal tract and that they originate in cortical mechanisms, though not necessarily on the motor side. "Relative integrity" of the pyramidal system is necessary to explain the continuity and activity of the movements. He stated: "I have never yet found a case of either [chorea or athetosis] in which spontaneous movements occurred in the presence of absolute corticospinal paralysis." Yet there is enough indication of "some defect of function" in chorea, and evidence is conclusive that "a degree of impairment of pyramidal function is not inconsistent with the appearance of athetoid movement." This is on the whole a somewhat unsatisfactory group of statements, especially in respect to the concept of "absolute corticospinal paralysis," a term which has been used also in regard to the abolition of parkinsonian tremor [3] and does not mean much when analyzed more closely. The fact that in clinical and experimental observations on decerebrate rigidity no athetoid movements were seen likewise is not conclusive, for a number of reasons. The abolition of unilateral athetosis by Horsley,[12] cited by Wilson to support his thesis, was accomplished by extirpation of area 6a, as is now known. Horsley stated that the specimen removed contained hardly any Betz cells. Area 4 in man can scarcely be removed without damage to adjacent areas. Bucy and Case [13] and a number of more recent workers [14] have repeated Horsley's operation and have intentionally removed area 6a or parts of it, often with considerable success.

While cortical extirpation of the projection areas of long extrapyramidal tracts has thus acted to alleviate, or even to abolish, the movements in athetosis, section of the anterolateral, subcorticospinal extrapyramidal tracts by one of us [15] led to a similar result. For this reason we feel more inclined to consider the extrapyramidal systems, and not the Betz cell projections, as the chief carriers of the motor impulses in cases of athetosis and chorea, in spite of a similarity of

12. Horsley, V.: The Linacre Lecture on the Function of the So-Called Motor Area of the Brain, Brit. M. J. **2**:125, 1909.

13. Bucy, P. C., and Case, T. J.: Athetosis: Surgical Treatment of Unilateral Athetosis, Arch. Neurol. & Psychiat. **37**:983 (May) 1937.

14. Putnam, T. J.: The Diagnosis and Treatment of Athetosis and Dystonia, J. Bone & Joint Surg. **21**:948, 1939.

15. Putnam, T. J.: Treatment of Athetosis and Dystonia by Section of Extrapyramidal Tract, Arch. Neurol. & Psychiat. **29**:504 (March) 1933.

management of motor units in these diseases and in normal voluntary movement. After many decades of research, too little is known of the actual way in which the intact pyramidal system influences movement to speak with certainty about it. It is generally assumed that part of the function of the pyramidal system consists of an inhibitory influence on reflex mechanisms and on antagonists, and it is possible that, as Wilson suggested, the simultaneous innervation of antagonists in cases of athetosis and chorea is the result of "pyramidal defect" in one respect while the pyramidal system still has an influence on the alternation of motor unit innervation. The actual impulses for the abnormal movement may, at the same time, be transmitted along the extrapyramidal pathways and stimulate whatever motor unit mechanism is best prepared to respond, according to a greater or less extent of damage done to the pyramidal tract, with consequent release of the motor systems of the cord.

The coexistence of alternating tremor and athetosis, sometimes in the same limb, presents an additional physiologic problem. It has been assumed [7] that tremor is one of the features of athetosis; indeed, athetosis was formerly often classified with the tremors. It is now believed that there is enough evidence to show that alternating tremor of the parkinsonian type is transmitted along other tracts than those active in athetosis and is impressed on the muscle by another mechanism. It has been shown by one of us [16] that parkinsonian tremor is not influenced by section of anterolateral extrapyramidal tracts in the cord. On the other hand, section of the lateral pyramidal tract in the cord and also extirpation of the extrapyramidal projection area 6a in the cortex have the effect of abolishing parkinsonian tremor, or at least of reducing it substantially. In cases of mixed symptomatology parkinsonian tremor has been seen to persist while the athetosis was considerably reduced by anterolateral chordotomy; in 1 instance the patient went back to work as a teacher in college. Alternating tremor is not a usual symptom of athetosis in its pure form. When it is present additional structures must be involved in the disease; in confirmation of this we have obtained a number of histories of intelligent patients in which the onset of the two manifestations was separated by an interval of several years.[17] Impulses for abnormal movement may thus be trans-

16. Putnam, T. J.: Relief from Unilateral Paralysis Agitans by Section of the Pyramidal Tract, Arch. Neurol. & Psychiat. **40**:1049 (Nov.) 1938; Surgical Treatment of Paralysis Agitans, ibid., to be published.

17. We are unable, from our material, to confirm Lindsley's [7] interpretation of his findings, namely, that rhythmic bursts of action potentials are of organic origin and irregular groups of "functional" nature. Nor do we believe on the basis of our material that this differential point could be used in athetosis, chorea, tic and torticollis.

mitted simultaneously, probably in all or in the majority of the long descending tracts, but they produce different motor disturbances. It is interesting to speculate about the fact that in cases of both athetosis and parkinsonian tremor integrity of the projections from area 6a seems to be usually necessary for the performance of the abnormal movement, while in both instances one other tract is involved in addition. No "tonic" rigidity was seen in patients with athetosis when at rest, while in patients with parkinsonian rigidity (and also in 1 with decerebrate rigidity) it was always seen. We may conclude, therefore, that the "released" basic innervation is not transmitted along the extrapyramidal projections of area 6a, but presumably has other pathways.

During this investigation only 2 cases of pure cerebellar tremor (i. e., not complicated by obvious spasticity) were studied.[3] In both instances the motor unit management was similar to that in normal muscles and in athetosis, as shown in figure 3. The material available is too limited to allow conclusions as to a similarity of performance of movement in athetosis and in cerebellar ataxia; clinical analogies exist, however, and Wilson has pointed out several possibilities of considerable theoretic interest.

Puzzling, again, is the fact that there is no evidence of abnormal impulses in potentials recorded from the brain in cases in which involuntary movements are conceivably mediated by cortical structures. It should be remembered, however, that normal volitional activity, presumably of cortical origin, cannot be recognized in electroencephalograms.

SUMMARY AND CONCLUSIONS

Action potentials of muscles in patients with athetosis and Sydenham's chorea have been studied. A number of features characteristic of the specific type of motor innervation in these diseases can be recognized by comparing records obtained from different motor units of one muscle in their relation to each other and to the whole muscle and also by comparing the behavior of antagonists in simultaneous leads. These relations are the same in both diseases, in spite of a number of clinical differences in characteristic cases.

1. Motor unit discharges are asynchronous and polyrhythmic in simultaneous leads during both involuntary and voluntary movements. In this respect they resemble normal voluntary innervation.

2. Antagonists are in almost constant, simultaneous innervation, which may be steady or irregular in either muscle, during both involuntary and voluntary movements.

3. During periods of rest no indication of basic or "tonic" innervation is noticed in the muscle.

4. During occasional periods of innervation of the protagonist alone no activity in the antagonist is seen. This seems to indicate that in cases of uncomplicated type the "stretch" reflex mechanism is not active, as in spasticity.

5. In cases in which spastic paraplegia is a complication a tendency to synchronous motor unit discharge is seen, but the simultaneous innervation of antagonists is the same in these cases as in those of pure athetosis.

6. Alternating tremor may be found as a complication of both diseases. This is considered to be caused by involvement of a different pathologic mechanism.

7. Mechanisms for the origin and transmission of the different types of involuntary movement and the motor unit management are discussed.

8. The relation of voluntary and normal innervation to different forms of motor disorder is discussed.

SPONTANEOUS CEREBRAL VENTRICULOSTIUM

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CHICAGO

The spontaneous development of an opening between the third ventricle or the lateral ventricles and the external surface of the brain is so unusual that the following 2 cases are reported. Such openings develop as a consequence of expansion of the cerebral ventricles when there is obstruction to the flow of cerebrospinal fluid. In the only such case with a pathologic study of the brain previously reported in the literature, the obstruction took place at the aqueduct of Sylvius. In the second case reported here the block was at the same site, and in the first case an enormous teratoid tumor in the posterior cranial fossa was responsible for the stoppage.

REPORT OF CASES

CASE 1.—Mrs. M. B., aged 54, who had been referred by Dr. H. T. Haver of Chicago, entered the Billings Hospital in the service of Dr. Percival Bailey on Aug. 12, 1937, in an extremely confused mental state. She dated all her symptoms to two days previously. From her family and through the courtesy of Dr. George W. Hall, of Chicago, the following history, beginning twelve years previously, was obtained.

The records of St. Luke's Hospital, Chicago, state that on Oct. 18, 1925, after a dinner party, the patient suddenly had a severe headache on the right side, accompanied with nausea and vomiting. She was confined to bed for the next four weeks with severe headaches, emesis two to four times a day and continuous diplopia. On November 14 an attempt to walk revealed a very unsteady gait, which became progressively worse until by December 15 she was unable to stand or walk without assistance. She was admitted to St. Luke's Hospital on Jan. 3, 1926, still having headaches but vomiting only occasionally. Dr. George W. Hall found that she was disoriented as to time and place and had paresis of the left facial and palatal muscles, deviation of the protruded tongue to the left, slight unsteadiness in the heel to knee test bilaterally and slightly irregular pupils which did not react well to light. The optic disks and extraocular movements were normal, according to Dr. E. V. L. Brown. The spinal fluid showed no cells, a negative Wassermann reaction and a faintly positive Pandy reaction; the initial pressure of the fluid was not measured. The patient was discharged as improved nine days later, with a diagnosis of probable cerebral glioma on the right; however, within a few weeks the defects in her memory and gait had practically disappeared.

On March 10 she was readmitted because of vomiting during the preceding three weeks. Aside from some lethargy, Dr. Hall noted no positive neurologic abnormalities, and the spinal fluid obtained at this admission was normal. She was observed no further at St. Luke's Hospital and was apparently well for nine years.

Late in 1935, the patient was found unconscious on the sidewalk and was black and blue from her head down to her hips on the right side posteriorly. She was

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dazed for about a week but recovered, with no noticeable paresis; she had amnesia for the episode. Two or three months later her gait became unsteady, and for one year before her admission to the Billings Hospital she staggered so much that she was unable to walk. The incoordination progressed to her upper extremities, so that she could neither write nor sew. For about one year there had been progressively more frequent incontinence of urine and feces. For about one month she had had dysphagia, and her speech had been slow, slurred and monotonous. Numerous other items in the clinical history were noncontributory to the neurologic disorder.

Neurologic Examination.—There were: (1) coarse horizontal nystagmus on looking a few degrees to either side, coarser on looking to the left; (2) generalized

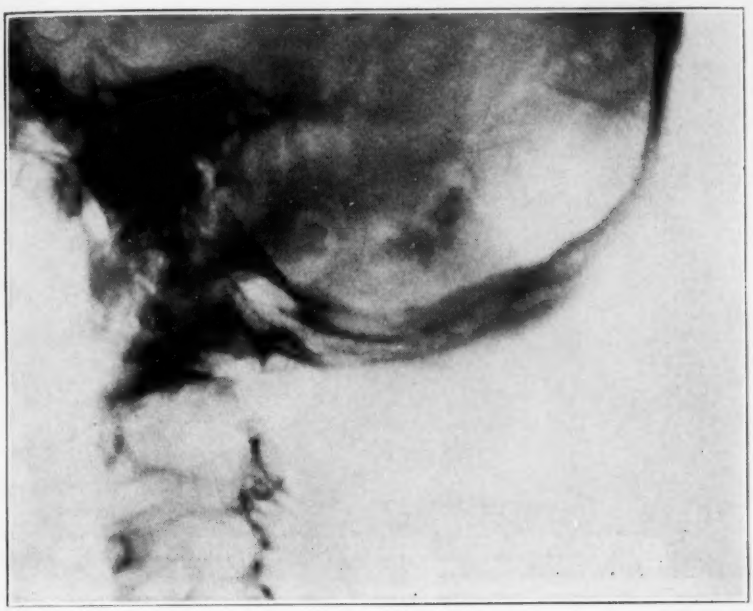

Fig. 1 (case 1).—Two large shadows of calcification in the posterior cranial fossa, with a smaller one behind and between them.

muscular weakness, especially marked in the intrinsic muscles of the hands, in both quadriceps muscles and in the dorsiflexor muscles of the left foot; (3) generalized hypotonia, about equal in the two arms, but more marked in the left than in the right leg; (4) ataxia in all four extremities, with intention tremor on finger to nose testing, more severe on the left than on the right, and dysmetria on the heel to knee test on each side; (5) grossly disturbed cerebration, with disorientation as to time and place, such poor concentration that testing of finer modalities of sensation was impossible, with some euphoria, and (6) hyperactive tendon reflexes, absent abdominal reflexes and a suggestively positive Babinski sign on the left. The left facial, palatal and glossal weakness noted in 1926 was absent, and the pupils reacted normally. The visual fields, visual acuity and optic disks were normal.

Roentgenograms of the skull (fig. 1) revealed a midline calcification in the posterior part of the posterior fossa. On lumbar puncture the initial pressure

of the spinal fluid was 165 mm.; the dynamics, Pandy reaction for globulin and Wassermann reaction of the spinal fluid were all normal; there were no cells; the Lange curve was 0000000000; the value for total protein was 20 mg. per hundred cubic centimeter. The Wassermann and Kahn reactions of the blood were negative.

Course.—Despite the unusual history, the marked cerebellar signs and calcification strongly suggested a neoplasm, but neither pneumencephalographic examination nor suboccipital exploration was carried out because of the patient's very poor general condition. She also had hypertension, bronchopneumonia and pyuria; acute pulmonary edema and hyperpyrexia developed on August 16, four days after entry, and the patient died the next day.

Autopsy.—This was performed one hour and twenty minutes after death. In addition to changes in the central nervous system, there were: (1) bronchopneumonia of the lower lobe of the left lung, edema of the other pulmonary lobes and focal fibrous pleuritis; (2) ascending bilateral pyelonephritis, with multiple retention cysts in the kidneys and left renal lithiasis, and (3) persistence of an unusual amount of thymus tissue, measuring 2 by 3 cm.

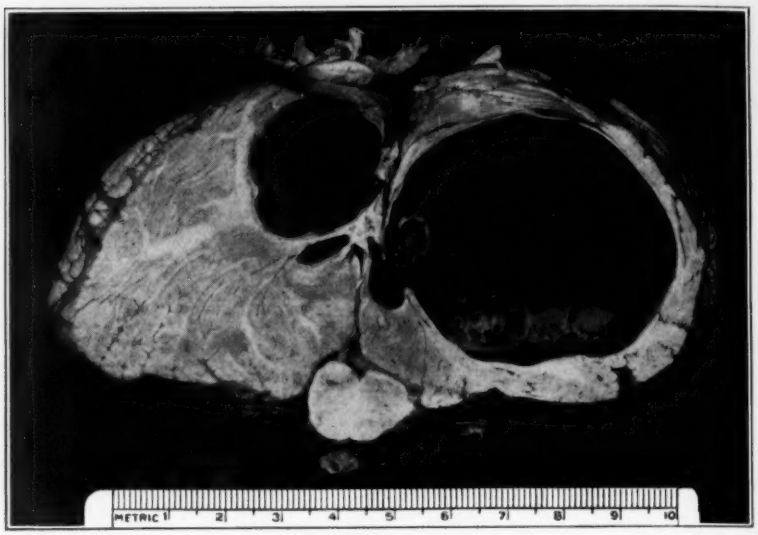

Fig. 2 (case 1).—Cross section through the cerebellum and brain stem, showing the tremendous extension of the tumor into the right cerebellar hemisphere and the moderate extension into the left hemisphere.

Examination of the brain showed as the principal observation an enormous multilocular cystic tumor occupying the cerebellar vermis and much of each cerebellar hemisphere (fig. 2). On section of the cerebellum the multiloculated cyst in the left hemisphere was seen to extend into the vermis, was filled with a brown, soft, solid material and measured 2 cm. in diameter. Posterior to the vermis were two more nodules; these were hard and black, each measuring 4 mm. in diameter. The right cerebellar hemisphere contained an enormous cyst, 5 cm. in diameter, filled with hard, black rubbery material. The contents of all of the cysts fell out,

maintaining their form as casts of the interior. The walls of the cysts were all smooth internally and fell away readily from the cerebellar tissue externally. All of the cysts were inside the dura mater, which was normal throughout.

There were flattening of the convolutions of the cerebral hemispheres and narrowing of the sulci. The lateral and third ventricles were only moderately dilated, the third ventricles being circular on coronal section, with a maximum diameter of 1.2 cm. The lamina terminalis was greatly thinned out, and Dr. A. Earl Walker noticed that there was an ostium here, about 4 mm. in diameter, between the third ventricle and the cisterna laminae terminalis (fig. 3).

On microscopic examination the cysts were lined by a single layer of columnar epithelium which in places was replaced by two, three or four layers of cells forming a modified stratified epithelium. About the epithelial lining was a fibrous capsule which, with the adjacent glial lining, completely separated the cysts from the adjoining cerebellar tissue and fourth ventricle. At the angle between the

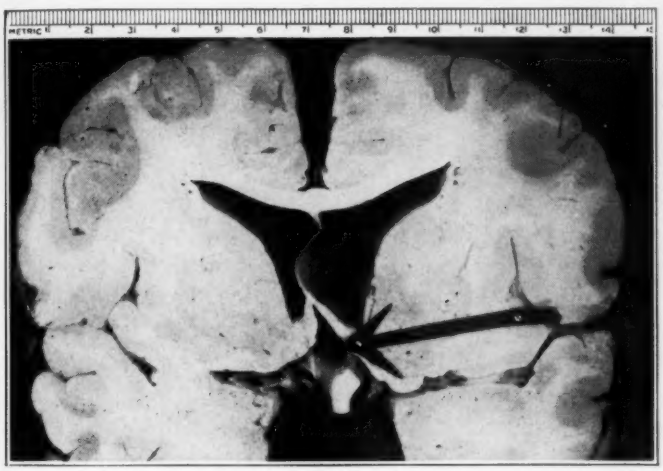

Fig. 3 (case 1).—Abnormal opening in the lamina terminalis (indicated by arrow). There is only moderate dilatation of the lateral ventricles.

inferior surface of the vermis and the posterior end of the fourth ventricle was a mass of tissue forming a nodule in the wall of a cyst. This tissue contained a fine network of reticulin and much collagenous fibrous connective tissue, but in between this material there were numerous irregular cords of epithelial cells containing no intercellular bridges. There were also several pieces of osseous tissue. Presumably these were responsible for the shadow seen in the roentgen film. One of these almost completely enclosed some fat cells, which suggested a rudimentary yellow marrow. There were several small collections of rudimentary hairs, and there was one group of five or six bundles of rudimentary muscle tissue, probably smooth rather than striated muscle. There were several glands with ducts leading to the principal cystic cavity, and in some areas there were numerous macrophages laden with fat and/or old blood pigment. In one area there were numerous long, narrow slits occupied in vivo by cholesterol crystals. No hairs or teeth were to be found in the cystic contents. There was no stratified squamous epithelium any-

where, and no keratohyaline granules were present. The absence of such epithelium and the presence of bone classified the tumor as a teratoid rather than a dermoid cyst.

Grossly and microscopically the spinal cord was normal.

Diagnosis.—The diagnosis was midline cerebellar teratoid tumor with moderate secondary hydrocephalus and rupture through the lamina terminalis.

Comment.—The most striking feature of the case, the complete subsidence of symptoms for nine years, is probably to be correlated with the abnormal opening observed in the lamina terminalis. It is unlikely that this was an artefact, because the brain was placed in solution of formaldehyde at once after its removal from the skull and was not disturbed until examination a week later, at which the defect was observed, and the margins of the lamina terminalis about the opening had been thinned to the point of transparency.

Furthermore, the findings on the patient's entry to the Billings Hospital did not indicate the increased intracranial pressure one would expect from such an enormous midline cerebellar tumor. She had no headaches, vomiting, papilledema or paresis of the abducens nerve, wheras headaches, vomiting and diplopia had all been prominent symptoms twelve years previously. On her last entry to the hospital the spinal fluid was under a pressure of only 165 mm. of water, and in the postmortem specimen the first three ventricles showed only the mild degree of enlargement that might have developed coincidentally with the initial accession of symptoms in 1925.

It might be suggested that the subsidence of the symptoms was due to spontaneous rupture of the cystic tumor. However, this explanation is not tenable, because there was no evidence of the cystic contents in the subarachnoid space, as is seen in cases of such rupture (Bauditz; Beneke; Erdheim; Helly; Lua; Raymond and his associates; von Tannenhain).[1] The cystic contents in these cases could not be absorbed but were dispersed in masses which in the chronic cases became surrounded by giant cells. Further, in my case the tumor was multilocular, and it is unlikely that enough locules would have broken simultaneously to cause all symptoms to disappear.

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1. Bauditz, A.: Ueber Dermoide und Epidermoide des Gehirns, Ztschr. f. d. ges. Neurol. u. Psychiat. **144**:135-147, 1933. Beneke: Zur Frage der meningealen Cholesteatome, Virchows Arch. f. path. Anat. **142**:429-446, 1895. Erdheim, J.: Ueber Hypophysenganggeschwülste und Hirncholesteatome, Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Cl. **113**:537-726, 1904. Helly, K.: Teratom im Kleinhirnwurm mit Steatose des Cerebrospinalliquor, Virchows Arch. f. path. Anat. **254**: 573-578, 1925. Lua, M.: Ein Fall von pialen Dermoidzysten mit Steatose der Gehirnkammern und des subarachnoideal Raumes, Deutsche Ztschr. f. Nervenh. **109**:212-230, 1929. Raymond, F.; Alquier, L., and Courtellemont, V.: Un cas de kyste dermoïd des centres nerveux, Rev. neurol. **12**:635-636, 1904. von Tannenhain, E.: Dermoidcyste des dritten Gehirnventrikels, Wien. klin. Wchnschr. **10**: 494-496, 1897.

Hence I believe that the patient's nine year period of freedom from symptoms was due to the spontaneous development of a third ventriculostium.[2] If this is what took place, it argues in favor of the similar operative procedure recommended by Dandy [3] and by Stookey and Scarff [4] for relief of hydrocephalus from occlusion of the aqueduct of Sylvius. The ventriculostium continued patent and functioning for nine years and was apparently still effective at the time of death.

The records of Dr. Percival Bailey include another case in which there was a spontaneous ventriculostium, but in this case the hydrocephalus was not relieved.

CASE 2.—G. T., a boy aged 14 years 11 months, entered the neuropediatric service of Dr. D. N. Buchanan at the Bobs Roberts Memorial Hospital on Jan. 27, 1933. He had had evident mental retardation for six years; during the first two years in school he did well, but in the succeeding six years he had advanced only two grades to the fourth grade. Obesity was first noticed two years before entry and had progressed; it was accompanied with an enormous appetite, especially for sweet foods. About one year before entry there began episodes of occipital pain of sudden onset in which the head was thrown back and maintained extended. On the mornings of days in which such episodes took place there was frequently vomiting. For five weeks he had had attacks in which the head was thrown back and the eyes were rolled up. These lasted a few minutes and were likely to recur at about hourly intervals, and after a few of them the speech became poorly enunciated. There was no loss of consciousness, and no convulsive movements occurred. For five weeks there had also been unsteadiness of gait and dimness of vision. For about the same length of time he had urinated frequently (up to every twenty minutes), but there was no polydipsia.

Examination.—The abnormal findings were: (1) excessive subcutaneous fat, with a prominent abdomen; (2) infantile external genitalia and very little hair over the body; (3) bilateral papilledema, of 2 to 3 D, in each eye, with secondary atrophy in the temporal quadrants; (4) absence of light perception in the right eye and 15/200 vision in the left eye; (5) widely dilated equal pupils (7 mm.), the left reacting sluggishly and only to direct light, the right reacting only consensually; (6) coarse rotary nystagmus in both eyes on looking to the left with fine rapid nystagmus in both eyes on looking to the right; (7) dimished corneal reflexes, the right weaker than the left; (8) deviation of the jaw to the left on

2. As commonly used in such words as gastrostomy, enterostomy and colostomy, the suffix "stomy" following an etymologic root indicating a structure means the operative establishment of a fistula in that structure. Although the suffix itself is derived from the Greek στομα, meaning mouth, and conveys no suggestion as to how the opening has been made, current usage has applied it only to operative intervention. Hence the word "ventriculostium" has been coined, the Latin word "ostium" (opening) being used as the suffix to differentiate this opening, which developed spontaneously, from the similar ones produced surgically.

3. Dandy, W. E.: Operative Procedure for Hydrocephalus, Bull. Johns Hopkins Hosp. **33**:189-190, 1922.

4. Stookey, B., and Scarff, J.: Occlusion of the Aqueduct of Sylvius by Neoplastic and Non-Neoplastic Processes with a Rational Surgical Treatment for Relief of the Resultant Obstructive Hydrocephalus, Bull. Neurol. Inst. New York **5**:348-377, 1936.

opening the mouth and bilaterally weak masseter muscles, the left weaker than the right; (9) facial weakness on the right on voluntary and emotional movement; (10) palatal paralysis on the right and palatal paresis on the left side; (11) absent palatal and pharyngeal reflexes on both sides; (12) dysphagia and dysarthria; (13) deviation of the protruded tongue to the left; (14) absence of abdominal reflexes in all four quadrants; (15) a positive Babinski sign on the right and an equivocally positive Babinski sign on the left; (16) on finger to nose testing an irregular action and terminal tremor on each side, which was worse on the left side; (17) in the sitting position continuous voluntary efforts to maintain the posture, with tilting of the head toward the right shoulder; (18) standing and walking on a wide base; (19) in the Romberg position with the eyes closed, loss of balance and falling, usually to the right, and (20) a cracked-pot sound on percussion of the enlarged head.

Roentgenograms of the skull revealed a generalized increase in digital markings and diastasis of the sutures. The roentgenograms of the optic foramens were normal. The basal metabolic rate on two successive days was + 33 per cent and + 31 per cent, respectively. A dextrose tolerance test gave normal results. The unrestricted fluid intake varied from 550 to 1,300 cc. on the five days; that is, no polydipsia was present.

Course.—On Feb. 1, 1933, the patient had a severe convulsion and remained semicomatose. A ventricular puncture on the left was performed to relieve the increased intracranial pressure. That evening he began to have peculiar attacks characterized by the development of patches of redness in the skin of the face, trunk and upper limbs and by spontaneous vertical nystagmus. The first attack lasted about five minutes and was not accompanied with involuntary movements. After the second attack the ventricle was again punctured, and again fluid escaped under a marked increase of pressure. In the early morning hours there were three more attacks of extensive flushing, unconsciousness, a faintly palpable pulse and a blood pressure so low it was unobtainable. Between attacks he was mentally alert and had a blood pressure of 90 to 100 systolic and 80 to 84 diastolic. Later in the morning he suddenly ceased breathing.

Clinical Diagnosis.—In view of the marked involvement of the posterior cranial nerves and the cerebellar seizures and signs, the clinical diagnosis was thought to lie between a cerebellar and a metencephalic tumor.

Autopsy.—This (restricted to the brain) was performed seven hours after death by Dr. A. E. Walker and Dr. P. C. Bucy, who found the primary source of difficulty to be a tumor of the brain stem. A conspicuous nodule of it lay in the midline of the tectum of the midbrain, between the superior colliculi and occluding the rostral portion of the aqueduct of Sylvius. The hard nodule of tumor was not sharply demarcated from the nerve tissue and measured about 6 by 8 mm. in its greatest cross section. There was an enormous dilatation of the first three ventricles and of the foramens of Monro. Corresponding to this hydrocephalus were flattened convolutions and narrowed sulci of the cerebral hemispheres and marked thinning of the anterior and inferior walls of the third ventricle. In the posteromedial part of the body of the right lateral ventricle was an abnormal opening measuring 6 by 8 mm. (fig. 4). It lay just anterior to the tip of the splenium of the corpus callosum and above the right crus of the fornix. Whereas normally the posterior portion of the body of the corpus callosum is in contact with the body of the fornix, the ventricular dilatation in this case had elevated the corpus callosum and pushed it so far posteriorly that it recurved anteriorly to the tip of the splenium. The fornix was nearer to this tip than to any other part of the corpus callosum but was separated from it by a full centimeter. The abnormal opening emptied into a large triangular

cavity, 2.2 by 2.0 by 3.5 cm. in midsagittal section. The base of the triangle was the anterior boundary of the cavity and was formed by the pineal body above and the corpora quadrigemina with the tumor below. The superior surface of the cerebellum was the inferior boundary, and the tentorium cerebelli was the superior boundary. The cavity did not communicate with the subarachnoid space, and the arachnoidal tissue which lined the posterior part of the cavity could be separated into two layers. The area between these two layers communicated with the subarachnoid space, as was demonstrated by injection of air into that space. With the exception of compression of the superior surface of the cerebellum and a compression cone formed by the downward herniation of the tonsils, the cerebellum was normal.

Microscopic examination of the tumor showed it to be a typical astrocytoma, composed of loosely scattered cells with round nuclei, a moderate amount of cyto-

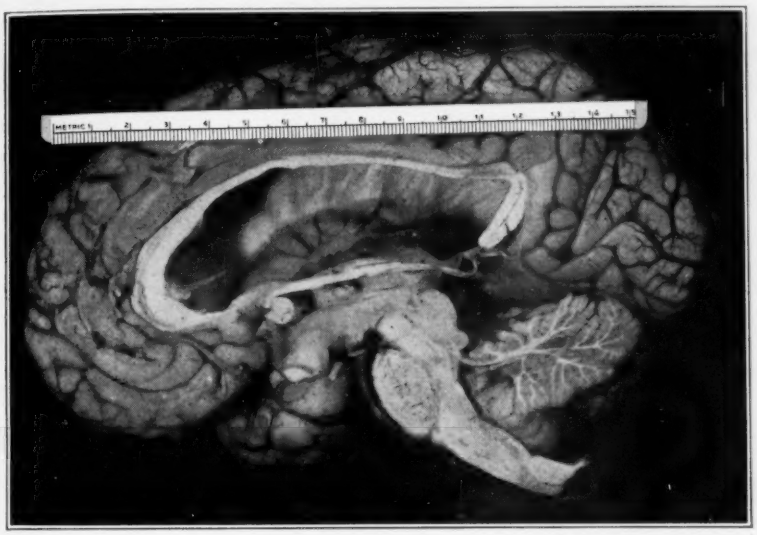

Fig. 4 (case 2).—Midsagittal section. The superior colliculus is enlarged by the tumor it contains. Great dilatation of the third and lateral ventricles is obvious. Just above and behind the superior colliculus the abnormal opening of the lateral ventricle is seen, and the abnormal cavity is below it and above the cerebellum.

plasm and branching processes. The neoplastic cells infiltrated without definite boundary into the normal tissue of the pons as well as the midbrain.

In addition to the foregoing observations related to the tumor, there was a small, thin-walled cyst filled with clear, colorless fluid lying beneath the optic nerves and the optic chiasm and spreading the former structures widely apart. Its largest cross section measured about 2 by 4 cm. Its posteroinferior aspect was connected with the hypophysis by a thin stalk.

Comment.—The signs of involvement of the structures in the posterior fossa were due not only to their invasion by the tumor but to the fact that they were not given the usual protection by the tentorium cerebelli; there was in effect a large, fluid tumor in the upper part of the posterior fossa. The widely dilated pupils showing no reaction to

direct light constituted the only sign which can be attributed with reasonable certainty to the destruction of tissue in the tectum mesencephali by the tumor. The obesity and retardation of sexual maturity were ascribed to secondary pressure on the hypothalamus and pituitary gland, with the resultant atrophy there. The extensive destruction of nerve tissue precluded any attempt to localize the site of origin of the interesting terminal cardiovascular attacks. The failure of the perforation of the lateral ventricle to be carried into the subarachnoid space prevented the patient from benefiting from it as did the patient in the previous case.

I know of only 2 other reports in the literature dealing with spontaneous ruptures from the ventricles to the surface of the brain. De Lange described a hydrocephalic child whose head at 5½ months of age reached a maximum circumference of 73 cm. and then gradually diminished to 51 cm. at 1 year and 10 months, at which time he died of pneumonia and meningitis. The aqueduct of Sylvius was occluded, and in the course of the succeeding ventricular enlargement a dorsolaterally directed channel developed from the anterior part of the body of each lateral ventricle. The right channel had reached the surface of the brain, and ventricular fluid had apparently been attaining the surface of the cortex by this route for some sixteen months. De Lange [5] and van Stockum [6] each described cases in which a hydrocephalic child experienced a sudden diminution in the size of the head to dimensions near the normal and remained clinically cured of the hydrocephalus.

In the 3 cases studied pathologically, the 1 of De Lange and my 2, one notes that the rupture took place through the cerebral cortex in the 2 children and that only in the adult did the lamina terminalis give way.

SUMMARY

Two cases are reported in which there was a spontaneous rupture connecting a ventricle with the surface of the brain. In the first case the rupture through the lamina terminalis permitted a remission in the patient's symptoms for nine years, and the abnormal ostium was still patent eleven years after the presumed time of its development. This case constitutes the longest clinical demonstration on record of the efficacy of ventriculostomy of the third ventricle for the relief of obstructive hydrocephalus arising from occlusion of the aqueduct of Sylvius or the fourth ventricle.

In the second case a rupture through the medial wall of one lateral ventricle did not relieve the patient's symptoms, since no communication was established with the subarachnoid space.

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5. de Lange, C.: Spontaneous Healing in a Case of Hydrocephalus, K. akad. v. wetensch. te Amsterdam, Proc. **32**:78-85, 1929.

6. van Stockum: Nederl. tijdschr. v. geneesk. **1**:543, 1910; cited by de Lange.[5]

ONE HUNDRED CASES OF A CONDITION DIAGNOSED AS ACUTE ENCEPHALITIS

A CLINICOPATHOLOGIC STUDY

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The diagnosis of encephalitis, particularly of certain types of encephalitides, has been frequently described as a "wastebasket clinical designation." [1] It is the aim of this study to contribute to available knowledge by a follow-up investigation of all the cases in which a diagnosis of encephalitis or encephalomyelitis was made clinically or at autopsy at the Boston City Hospital from 1928 to and including 1938.

MATERIAL

The group examined consisted of 100 patients. The total hospital admissions during the same period were 368,000. Patients suffering from postencephalitic parkinsonism, Sydenham's chorea and syphilis of the central nervous system were not included in the group. Of the 100 patients studied, 45 were in the Neurological Unit, while the remaining 55 were distributed in the various services of the Boston City Hospital. Thirty-seven died in the hospital; for 19 of these complete autopsy reports and microscopic slides were available. Thirty-six of the remaining 63 patients could be reexamined at the Boston City Hospital. The year of reexamination was 1938 or 1939. Data on an additional 14 patients were furnished by the home physician and a social worker. Twelve other patients stayed long enough in the hospital to justify a conclusion concerning the nature and course of their disease, though they were not available for reexamination. In 6 cases, in 4 of which the patients were admitted in a comatose condition and died within the first days and in which there was a question of encephalitis, the clinical data were not sufficient to make a definite diagnosis. Of the 100 patients, 62 were males and 38 females.

CLASSIFICATION

In the present state of knowledge any definition or classification of "encephalitis" or "encephalomyelitis" is, to some extent, necessarily unsatisfactory. A broad concept was assumed for the purposes of this investigation, with overlapping of the group of diseases which has been designated "encephalopathy." The diagnosis of "encephalitis" or

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Cooperation was given the author by Dr. Tracy J. Putnam, who suggested the investigation.

From the Department of Neurology, Harvard Medical School, and the Neurological Unit, Boston City Hospital.

1. Grinker, R. R.: Neurology, Springfield, Ill., Charles C. Thomas, Publisher, 1937.

"encephalomyelitis" was accepted, in the first place, when the histologic syndrome of "alteration, proliferation and exudation," to which Spielmeyer [2] preferred to restrict the terms encephalitis and encephalomyelitis, was observed at autopsy. This would include such conditions as post-measles encephalomyelitis, if characterized by the typical picture of perivascular demyelination and proliferation of glia cells and occasionally hematogenous elements. It should be emphasized, however, that inflammation is by no means synonymous with infection. Similar changes can be observed in the neighborhood of softenings, tumors and other gross lesions. They have also been produced experimentally by Putnam; [3] Rivers and Schwentker; [4] Hoefer, Putnam and Gray,[5] and others. Putnam and Alexander,[6] who produced the aforementioned changes by venular obstruction, used the term "encephalomyelitic reaction" for this syndrome. The neuropathologic picture may well be named "proliferative" encephalitis or encephalomyelitis, to differentiate it from other types of encephalitides.

Many investigators, among them Spielmeyer, have pointed out, however, that the same underlying disease may produce an inflammatory reaction or vascular disturbances in some cases and alteration of the ganglion and glia cells in others. Any of these components may assume the prevailing, or even exclusive, role. This is shown in the large group of "toxic" encephalitides, as they have been described, for example, by Grinker and Stone,[7] Low [8] and Ferraro and Scheffer.[9] Common features described by the authors are congestion of cerebral vessels, more or less profound, diffuse destruction of ganglion and glia cells and absence of perivascular demyelination.

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2. Spielmeyer, W.: Infektion und Nervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:161, 1930.

3. Putnam, T. J.: Studies in Multiple Sclerosis: "Encephalitis" and Sclerotic Plaques Produced by Venular Obstruction, Arch. Neurol. & Psychiat. **33**:929 (May) 1935.

4. Rivers, T. M., and Schwentker, F. F.: Encephalomyelitis Accompanied by Myelin Destruction Experimentally Produced in Monkeys, J. Exper. Med. **61**: 689, 1935.

5. Hoefer, P. F. A.; Putnam, T. J., and Gray, M. G.: Experimental "Encephalitis" Produced by Intravenous Injection of Various Coagulants, Arch. Neurol. & Psychiat. **39**:799 (April) 1938.

6. Putnam, T. J., and Alexander, L.: Disseminated Encephalomyelitis: A Histologic Syndrome Associated with Thrombosis of Small Cerebral Vessels, Arch. Neurol. & Psychiat. **41**:1087 (June) 1939.

7. Grinker, R. R., and Stone, T. T.: Acute Toxic Encephalitis in Childhood: Clinicopathologic Study of Thirteen Cases, Arch. Neurol. & Psychiat. **20**:244 (Aug.) 1928.

8. Low, A. A.: Acute Toxic (Nonsuppurative) Encephalitis in Children, Arch. Neurol. & Psychiat. **23**:696 (April) 1930.

9. Ferraro, A., and Scheffer, I. H.: Toxic Encephalopathy in Measles, Arch. Neurol. & Psychiat. **27**:1209 (May) 1932.

Between the two extremes of "proliferative" encephalomyelitis and encephalitis, on the one hand, and "toxic" encephalitis, on the other, are such conditions as those seen after chickenpox, described by Zimmerman and Yannet,[10] in which perivascular demyelination was noted without any glial proliferation, "hemorrhagic" encephalitis, chiefly observed after influenza, in which scattered foci of proliferated glia may be present, and some rarer entities.

The diagnosis of the infectious type of encephalitis and encephalomyelitis, in which the micro-organism can be cultivated from the nerve tissue, seems to be justified without further discussion. This entity merges, however, in cases of purulent encephalitis, into that of meningitis.

In addition, in the present study a final clinical diagnosis of encephalitis or encephalomyelitis was made when the history, signs and symptoms, laboratory findings, particularly those in the spinal fluid, and the further course, as observed on examination, corresponded with an accepted syndrome which, in other instances, was confirmed by observations at autopsy. Particular attention was paid to the spinal fluid findings during the course of the disease.

Table 1 gives a statistical account of the various groups.

POSTINFECTIOUS ENCEPHALITIS AND ENCEPHALOMYELITIS

In the group of cases of this type are included all those in which the cerebral disorder occurred during or immediately after a definite infectious disease, with the exception of cases in which an obvious local infection (meningitis, abscess or purulent encephalitis) could be demonstrated—for instance by culture. It will be seen that the cases fall into two subgroups, almost irrespective of the cause: those of the proliferative and those of the toxic type.

Pneumonia Encephalitis.—Proliferative Encephalitis (tables 2 and 3): It may be noted from the tables that abnormalities of the spinal fluid were associated with definite signs of localized neurologic lesions in all 3 cases of the proliferative type. Neuropathologic specimens (case 44) showed marked perivascular demyelination and infiltration, hyperemia and hemorrhages. Many of the cells around vessels and throughout the brain tissue were polymorphonuclear. The microscopic picture in this case closely resembled that of equine encephalomyelitis in man and will be published separately. No microscopic slides were available in case 53. Only 1 of this group of 3 patients recovered (case 33).

The changes observed at autopsy were obviously those of "proliferative" encephalitis. This syndrome differs not only pathologically but also clinically and in the spinal fluid picture from the "toxic" encepha-

10. Zimmerman, H. M., and Yannet, H.: Nonsuppurative Encephalomyelitis Accompanying Chickenpox, Arch. Neurol. & Psychiat. **26**:322 (Aug.) 1931.

litides in the following group, although in all cases pneumonia was the underlying disease.

Toxic Encephalitis (tables 4 and 5): Of the remaining 8 patients with encephalitis, 2 recovered (cases 12 and 19). In all 8 cases the clinical picture was that of diffuse cerebral involvement, shown by twitchings of the arms and legs, stiffness of the neck, Kernig's sign

TABLE 1.—*Incidence and Death Rate in the Individual Groups of Cases in Which a Diagnosis of Acute Encephalitis or Encephalomyelitis Was Made Between 1928 and 1938*

Condition	Number of Cases	Number of Deaths
Postinfectious encephalitis and encephalomyelitis following:		
Pneumonia	11	8
Infection of the upper part of the respiratory tract	8	2
Measles	2	2
Rubella	3	..
Mumps	1	..
Vaccination against variola	2	..
Vaccination against rabies	1	..
Acute enteritis	1	1
Erysipelas	1	..
	30	13
Unclassified encephalitis and encephalomyelitis	2	..
Cases in which multiple sclerosis developed	5	..
Diffuse periaxial encephalitis	2	..
Toxic encephalitis caused by exogenous poisons:		
Alcohol	4	1
Arsphenamine	2	..
Salicylic acid	1	..
Lead	1	..
	8	1
Infectious encephalitis:		
Due to otitis media or mastoiditis	3	2
Suppurative, after fracture of skull	3	3
Pneumococcic	2	2
Due to trichina	1	..
Tuberculous	1	..
Due to typhus fever	1	..
	11	7
Primary infections of the central nervous system (portal of entrance unknown):		
Acute lethargic encephalitis	4	1
Post-traumatic nonsuppurative encephalitis	2	..
Erroneous diagnosis of encephalitis	30	10
Unclear cases	6	5
Total	100	37

and, in children, occasionally convulsions. It should be emphasized that transient pareses, which occur frequently after convulsions, cannot be considered evidence of localized neurologic lesions. In this group the spinal fluid was normal. The histologic picture was that of diffuse hyperemia of the central nervous system, with or without perivascular hemorrhages (cases 38, 40 and 51). These 8 cases belong to the syndrome of "toxic encephalitis."

Perivascular infiltration was absent except for a few scattered mononuclear cells around isolated vessels and some emigration of leukocytes into the hemorrhagic lesions in 2 cases (38 and 51). These cases may

TABLE 2.—*Proliferative Encephalitis (After Pneumonia); Cases With Autopsy Records*

Case	Age	Sex	Year	Clinical Diagnosis	Autopsy Observations	Signs and Course	Spinal Fluid
44	23	M	1936	Pulmonary tuberculosis; meningitis	Bronchopneumonia; encephalitis. Marked cuffing, consisting chiefly of polymorphonuclear cells; hemorrhages; thrombi; perivascular demyelination; many gitter cells	Chills, cough, malaise and diarrhea. On thirteenth day drowsiness, stiff neck, headaches, right hemiparesis, bilateral ankle clonus; pneumococcus type VII in sputum; death 21st day	Initial pressure 190 mm. of water; cloudy; total protein 156 mg. per 100 cc.; cells 1,873 per cu. mm.; 93% polymorphonuclear leukocytes; sugar 82 mg. per 100 cc.; chloride 628 mg. per 100 cc.; colloidal gold curve 0011110000
53	17	M	1936	Acute encephalomyelitis; brain tumor?	Bronchopneumonia; acute encephalitis	One day before entry head cold and headaches. Unconsciousness; spasticity of extremities; hyperactivity of reflexes; bilateral Babinski sign; clonic convulsive movements. Temperature on admission 105 F. Death on next day	Initial pressure 130 mm. of water; cloudy; total protein 112 mg. per 100 cc.; cells 30 per cu. mm.; 84% polymorphonuclear leukocytes; 1,630 erythrocytes per 100 cc.; sugar 74 mg. per 100 cc.

TABLE 3.—*Proliferative Encephalitis (After Pneumonia); Recovery*

Case	Age	Sex	Year	Clinical Diagnosis	Final Diagnosis	Signs and Course	Spinal Fluid	End Result
33	27	M	1935	Encephalomyelitis, cause unknown	Post-pneumonia encephalitis	Pneumonia of six days' duration, which was resolving when severe headaches began. On admission nystagmus, blurred fundi and adiadokokinesis; Babinski, Oppenheim and Chaddock signs present. Two days after admission bilateral otitis media developed. Paracentesis was performed the following day with ensuing healing. Neurologic signs disappeared within a few days	Initial pressure 450 mm. of water; cloudy; total protein 124 mg. per 100 cc.; cells 580 per cu. mm.; 75% polymorphonuclear leukocytes; sugar 70 mg. per 100 cc.; chloride 720 mg. per 100 cc.; colloidal curve 0012100000; after two days: total protein 84 mg. per 100 cc.; cells 70 per cu. mm.; after six days: total protein 34 mg. per 100 cc.; cells 3 per cu. mm.	Headaches occasionally, patient otherwise well; fundi blurred and Oppenheim sign on the left

TABLE 4.—*Toxic Encephalitis (After Pneumonia); Cases with Autopsy Records*

Case	Age	Sex	Year	Clinical Diagnosis	Autopsy Observations	Signs and Course	Spinal Fluid
40	39	M	1930	Lethargic encephalitis	Bronchopneumonia; cerebral vessels generally injected, with perivascular edema; no other neuropathologic changes	Two weeks before admission cyanosis and drowsiness; rales over bases of lungs; nystagmus, coarse tremor of hands (11 years ago had lethargic encephalitis)	Initial pressure 600 mm. of water; cells 5 per cu. mm.
48	4	M	1929	Lobar pneumonia; encephalitis?	Bronchopneumonia; head not examined	Fever for 1 week; various aches and pains. Pneumonia on admission; temperature 102 F.; sluggish pupillary reaction; retraction of neck; possible Kernig sign	Normal
38	38	M	1935	Lobar pneumonia	Old abscess of lung; organizing pneumonia; hemorrhagic encephalitis. Some parenchymatous hemorrhages, with lymphocytic and polymorphonuclear immigration into these; occlusion of some small vessels; cultures of blood, abscess and brain sterile; Streptococcus viridans in lungs	Dyspnea for years; for 1 week cough, chills, intermittent delirium; death after 9 days	Not examined
51	20	F	1935	Acute encephalitis(?); drug ingestion(?); terminal bronchopneumonia	Bronchopneumonia. Perivascular hemorrhages in brain; few vessels surrounded by some mononuclear leukocytes; perivascular edema	Unconscious on admission presumably after ingestion of unknown drug; areflexia; blurred fundi; pneumonia (Pneumococcus type VI); death 3d day	Initial pressure 250 mm. of water; total protein 39 mg. per 100 cc.; cells 0; sugar 86 mg. per 100 cc.; chloride 685 mg. per 100 cc.; colloidal gold curve 0112110000

TABLE 5.—*Toxic Encephalitis (After Pneumonia); Recoveries and Cases Without Autopsy*

Case	Age	Sex	Year	Clinical Diagnosis	Final Diagnosis	Signs and Course	Spinal Fluid	End Result
12	20	F	1935	Toxic encephalitis after lobar pneumonia	Toxic encephalitis after lobar pneumonia	Lobar pneumonia (Pneumococcus type I); no fever in second week; during third week twitching of fingers and masklike face; slight delirium; after a few days, recovery	Not examined	Occipital headaches, dizzy spells
19	4	F	1936	Lobar pneumonia; acute hemorrhagic encephalitis	Toxic encephalitis during lobar pneumonia	Two days before admission fever and backaches; on admission temperature 103 F.; lobar pneumonia, with drowsiness, retraction of neck and positive Kernig sign; after 4 days, recovery	Total protein 21 mg.; sugar 65 mg.; chloride 684 mg., per 100 cc.; cells not counted	Headaches; knee and arm jerks more active on left than on right
61	45	F	1937	Lobar pneumonia; toxic encephalitis	Lobar pneumonia; toxic encephalitis	Lobar pneumonia; temperature 103 F., delirium, twitching of arms and legs, hyperactivity of reflexes and positive Chvostek's sign	Total protein 23 mg. per 100 cc.; cells 8 per cu. mm.; sugar 96 mg.; chloride 746 mg., per 100 cc.; colloidal gold curve 0100000000	Death 2 days after admission
63	6	M	1937	Acute encephalitis	Toxic encephalitis during pneumonia	Cough, cyanosis, dyspnea and fever 1 day before admission; after 24 hours sudden stiffness and drowsiness; on admission semicoma, with temperature 103 F. and increased to 106 F.; bronchial breathing, with rales over lungs	Pandy reaction negative; cells 1 per cu. mm.	Death 3 days after admission

represent borderline conditions between toxic and proliferative encephalitides. It should be noted that the encephalitis was complicated by an abscess of the lung in case 38 and by the ingestion of a poison prior to development of the pneumonia in case 51. The lesions in case 51 may have been caused by the poison as well as by the pneumonia or by both. Whether this case should be classified under postinfectious encephalitides or those caused by exogenous poisons is, therefore, a matter of choice.

In 5 of the 11 cases of encephalitis complicating pneumonia a diagnosis of "encephalitis of unknown origin" was originally made, in spite of the pneumonia which in all instances was present before or at the same time as the neurologic signs.

Pneumococcus type I was recovered from the sputum in 1 case of benign toxic encephalitis, and Pneumococcus types VI and VII in a case of fatal toxic and in a case of fatal proliferative encephalitis, respectively. The 3 patients who recovered had lobar pneumonia, whereas bronchopneumonia was predominant among those who died. On reexamination, all 3 of the patients who had had encephalitis complained of headaches. Only minute neurologic abnormalities could be found.

A few similar cases were cited by Comby [11] and by Ford.[12]

Since approximately 18,000 cases of pneumonia were recorded for the same period at the Boston City Hospital, the percentage of cases in which encephalitis and encephalomyelitis complicated pneumonia is 0.06 per cent. The percentage of cases of postmeasles encephalitis and encephalomyelitis reported ranged from 0.1 to 0.5 during various epidemics.

Encephalitis After Infection of the Upper Respiratory Tract (tables 6 and 7).—In 8 cases of encephalitis there was a history of "colds" or infection of the frontal or ethmoid sinuses from four to twelve days before the onset of neurologic signs. No particular trends can be recognized in the kind of infection, symptoms of which were chills, running nose, headaches and sore throat. In all cases stiffness of the neck and headaches were present at the onset, except in case 13, that of a child aged 5 years, in which "restlessness" before the onset of convulsions was noted. In 5 of the 7 cases there was involvement of the optic and oculomotor nerves, as shown by haziness or choking of the fundi, blurring of vision, palsy of the oculomotor nerves and paretic nystagmus. The spinal fluid was altered in all cases, the predominant type of cells being lymphocytes. The changes in the spinal fluid were not more marked in the cases of fatal termination than in those of the benign form.

11. Comby, M. T.: Les encéphalites aiguës postinfectieuses de l'enfance, Paris, Masson & Cie, 1935.

12. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, Springfield, Ill., Charles C. Thomas, Publisher, 1937.

TABLE 6.—*Encephalitis After Infection of the Upper Part of the Respiratory Tract; Cases with Autopsy Records*

Case	Age	Sex	Year	Clinical Diagnosis	Autopsy Observations	Signs and Course	Spinal Fluid
45	17	M	1928	Acute encephalitis	Diffuse encephalitis with perivascular hemorrhages and perivascular collection of mononuclear and gitter cells; perivascular demyelination	Cold, running nose, cough for a week; 1 day before onset headaches, sore throat, temperature 100 F.; on admission convulsions, spasticity of all muscles, patellar and ankle clonus and Babinski sign bilaterally	Initial pressure 170 mm. of water; total protein 69 mg. per 100 cc.; cells 160 per cu. mm.; 1% polymorphonuclear leukocytes; sugar 98 mg.; chloride 724 mg. per 100 cc.
47	28	M	1935	Encephalomyelitis, cause unknown	Acute hemorrhagic leukoencephalitis; perivascular cuffing with lymphocytes and polymorphonuclear leukocytes; occasional hemorrhages without cell reaction; foci of leukocytes with no relation to blood vessels; no considerable damage to nerve cells; meninges free	Cough and sore throat, with headaches and chills 1 week before admission; delirium 2 days before admission; pupils contracted, right facial paresis, weakness of right arm and leg; increase of deep reflexes on right; neck stiff, Kernig's sign bilaterally	Initial pressure 210 mm. of water; clear; total protein 74 mg. per 100 cc.; Pandy reaction positive; cells 175 per cu. mm.; 80% lymphocytes; sugar 74 mg.; chloride 756 mg. per 100 cc.

TABLE 7.—*Encephalitis After Infection of the Upper Part of the Respiratory Tract; Recoveries*

Case	Age	Sex	Year	Clinical Diagnosis	Final Diagnosis	Signs and Course	Spinal Fluid	End Result
4	34	M	1935	Encephalomyelitis, cause unknown	Encephalomyelitis after infection of the upper respiratory system	Six days before admission cough and head cold and then chill; staggering gait, slight stiffness of neck, clumsiness, bilaterally; retention of urine, tremors, muscle strength in legs diminished; patient alcoholic	Initial pressure 70 mm. of water; total protein 135, 70 mg. per 100 cc.; cells 210, 30 per cu. mm.; 5% polymorphonuclear leukocytes; sugar 74, 54 mg. per 100 cc.; chloride 632, 582 mg. per 100 cc.; colloidal gold curve 1222321000	Tremors; urgency to urinate; left pupil larger than right
13	5	M	1934	Encephalitis	Encephalitis after infection of the upper respiratory system	Two weeks before onset of cold, nose full of mucus, fever; clonic spasms on left side; slight weakness of left arm and leg on discharge	Initial pressure 195, 110 mm. of water; total protein 31, 23 mg. per 100 cc.; cells 132, 2 per cu. mm.; 27% polymorphonuclear leukocytes; sugar 64 mg. per 100 cc.; chloride 687, 788 mg. per 100 cc.; colloidal gold curve 0100000000 (final lumbar puncture seven days after admission)	Seizures; change in reflexes; after attack weakness and numbness of left side
17	35	F	1937	Encephalitis	Encephalitis after sinus infection	Double vision, blurring of vision for 2 months; drowsiness, weakness, aching of muscles and joints for last 7 days; tenderness over all sinuses; roentgenogram cloudiness, with infection of frontal and ethmoid sinuses; patient acutely ill; early choking of fundi bilaterally; slight weakness of left rectus muscle; neck slightly stiff; bilateral Kernig's sign	Initial pressure 220 mm. of water; total protein 52 mg. per 100 cc.; 5 polymorphonuclear leukocytes and 8 lymphocytes per cu. mm.; sugar 60 mg. per 100 cc.; chloride 651 mg. per 100 cc. (nine days after onset)	Headaches; dizziness, impaired finger to nose test; pain on tapping forehead
18	22	F	1934	Meningoencephalitis	Meningoencephalitis after infection of the respiratory tract	Ten days before onset of infection of upper respiratory tract, with sore throat, cough, general malaise, no fever; diplopia, headaches, stiff neck, nystagmus, ptosis of left lid and bilateral Babinski sign; on discharge only Babinski sign present	Initial pressure 3,260 mm. of water; total protein 340, 18 mg. per 100 cc.; cells 400, 7 per cu. mm.; 77% of polymorphonuclear leukocytes; sugar 56, 84 mg. per 100 cc.; chloride 656, 750 mg. per 100 cc.	Patient tires easily; sometimes paresthesia of left arm; dragging feeling in left leg; ankle jerk absent on left: Oppenheim sign on left; feels a "strain in her head"
100	34	M	1933	Acute encephalitis?; brain tumor suspected	Encephalitis after infection of the upper respiratory tract	Four days before onset head cold, sore throat, shivering; temperature on admission 102 F.; stiff neck, drowsiness, blurred vision, papilledema, weakness of the right facial nerve, central types	Initial pressure 250 mm. of water; total protein 45, 25 mg. per 100 cc.; cells 135, 10 per cu. mm., lymphocytes; sugar 55, 62 mg. per 100 cc.; chloride 717 mg. per 100 cc.; colloidal gold curve 1123332100	On discharge no headaches and less choking of disks; marked improvement
21	32	F	1935	Encephalomyelitis, cause unknown	Encephalomyelitis after infection of the upper respiratory system	Seven days before admission infection of upper respiratory tract developed, with headaches, malaise, running nose, nasal obstruction, paralysis of legs, paresthesia of limbs, optic neuritis and bladder trouble	Initial pressure 75 mm. of water; total protein 726 mg. per 100 cc.; cells 366 per cu. mm.; sugar 43 mg. per 100 cc.; chloride 682 mg. per 100 cc.; colloidal gold curve 0012342222	Bladder trouble, slight atrophy of the optic nerve; spastic gait; Babinski sign bilaterally; normal spinal fluid

Six of the 8 patients recovered, but the residuals were more severe than those following encephalitis complicating pneumonia. The child (case 13) continued to have seizures. Histologic examination in 2 cases (45 and 47) showed a striking picture of proliferative encephalitis, with dense perivascular cuffings consisting of lymphocytes and polymorphonuclear leukocytes, and hemorrhages. The clinical picture and the changes in the spinal fluid suggest that the 6 remaining patients who recovered had an analogous neuropathologic syndrome of proliferative encephalitis. The pathologic lesions in case 47, however, were somewhat different from those in the remaining cases of postinfectious encephalitis. There were many polymorphonuclear cells in the perivascular infiltrates, and some foci of infiltrating cells had no apparent connection with blood vessels. This relates the condition to the St. Louis type of encephalitis and to equine encephalomyelitis. There was, however, no meningeal condition and no considerable damage to nerve cells.

In no case was the connection between infection of the upper respiratory tract and encephalitis expressed in the original clinical diagnosis. The encephalitis was labeled as of "unknown origin."

Few cases have been reported in the literature [13] in which the apparently causal connection between infection of the upper respiratory tract and encephalitis was pointed out. It is frequently difficult to draw the line between this group of cases and those of acute multiple sclerosis. This point will be considered later.

Other Cases of Postinfectious Encephalitis (tables 8 to 12).—A few cases of involvement of the nervous system following rubella are known. The latest to be reported are those of Comby [11] and Ford.[12] Two of the 3 cases summarized here have been described by Merritt and Koskoff.[14] The signs and symptoms were identical with those which may occur after measles, pneumonia and other acute infections. The 3 cases conform with those of "proliferative" encephalitis after other infectious diseases. Neuropathologic changes indicate that there is every reason to believe that the lesions in these cases were identical with those of proliferative encephalitis after measles.[15] The case reported by Ford,

13. Greenfield, J. C.: Acute Disseminated Encephalomyelitis as Sequel to "Influenza," J. Path. & Bact. **33**:453, 1930. Grinker, R. R., and Bassoe, P.: Disseminated Encephalomyelitis: Its Relation to Other Infections of the Nervous System, Arch. Neurol. & Psychiat. **25**:723 (April) 1931. Davison, C., and Brock, S.: Acute Demyelinating Encephalomyelitis Following Respiratory Disease, Bull. Neurol. Inst. New York **6**:504, 1937.

14. Merritt, H. H., and Koskoff, Y. D.: Encephalomyelitis Following German Measles, Am. J. M. Sc. **191**:690, 1936.

15. Briggs, J. F.: Meningoencephalitis Following Rubella, J. Pediat. **7**:609, 1935.

however, in which the spinal fluid was normal and there were signs of more diffuse involvement of the nervous system, suggests that neurologic signs after rubella may be caused by toxic as well as by proliferative lesions of the nervous system.

Changes characteristic of both toxic and proliferative encephalitis can also be found in the neurologic complications after measles. The 2 children in this group died, and autopsy showed the typical picture of proliferative encephalitis following measles, which has frequently been described. Cases of postmeasles encephalitis are known,[9] however, in which no infiltrations were observed in the nervous system, but only changes attributable to the action of a toxin. The clinical picture was that of diffuse involvement of the nervous system, without any definite localizing signs. The spinal fluid had a normal protein content and moderate increase in cells.

Toxic encephalitis developed after mumps in 1 child (case 81). The signs were those of diffuse involvement of the brain. The spinal fluid was normal. On the other hand, autopsy material has been reported with lesions similar to those of proliferative encephalitis after measles.[16] It should be mentioned that an increase of cells in the spinal fluid has been observed in as high as 50 per cent of patients suffering from mumps, with or without neurologic signs. Three such cases will be discussed in the section dealing with erroneous diagnoses of encephalitis.

Toxic encephalitides like that complicating erysipelas may occur during the course of any disease which produces a toxin. No permanent structural alterations of the nervous system are known to occur after erysipelas.

Cases of encephalitis following acute enteritis have been reported by Comby,[11] in some of which definite localizing signs of lesions of the nervous system were described. Studies of the spinal fluid and autopsies were not made in her cases. The case (no. 50) reported here is a typical example of toxic encephalitis, with absence of infiltration in the brain, normal spinal fluid, except for a moderate increase of cells, and the clinical signs of diffuse involvement of the nervous system.

The data in my 3 cases of nervous complications after vaccination do not suffice to demonstrate a correlation of the laboratory findings, the clinical picture and the autopsy observations in cases of this syndrome.

In cases reported in the literature with autopsy reports the histologic picture closely resembles that described for postmeasles encephalitis. The typical demyelination may occur without glial proliferation or infiltration.[6]

16. Wegelin, C.: Ueber Meningoencephalitis bei Mumps, Schweiz. med. Wchnschr. **65**:249, 1935.

TABLE 8.—*Proliferative Encephalitis Following Measles; Cases with Autopsy Record*

Case	Age	Sex	Year	Clinical Diagnosis	Autopsy Observations	Sign and Course	Spinal Fluid
42	4	M	1930	Encephalitis following measles	Large subdural hemorrhage on the left; marked perivascular infiltration with polymorphonuclear, but chiefly mononuclear leukocytes; vessels filled with blood; few small hemorrhages in white matter; perivascular demyelination	Measles 6 days previously, rash 3 days later; patient not very ill, seemed to be recovering. On day of admission suddenly comatose; several convulsions on right side; pupils equal with normal reactions; macular rash	Initial pressure 400 mm. of water; clear; cells 95 per cu. mm., chiefly lymphocytes; globulin "not increased"
43	6	M	1936	Measles encephalitis; bronchopneumonia	Bronchopneumonia. Perivascular hemorrhages and mononuclear infiltration; few thrombi; perivascular demyelination	One day after eruptions restlessness, headache, vomiting; loss of speech; Kernig's sign bilaterally; loss of reflexes in lower extremities	Initial pressure 350 mm. of water; total protein 100 mg. per 100 cc.; cloudy; cells 55 to 65 per cu. mm.; 20 to 8% polymorphonuclear leukocytes

TABLE 9.—*Encephalitis Following Rubella; Recoveries*

Case	Age	Sex	Year	Clinical Diagnosis	Final Diagnosis	Signs and Course	Spinal Fluid	End Result
27	9	F	1935	Postrubella encephalitis	Postrubella encephalitis	Four days before admission rubella rash, which cleared up 2 days afterward. Onset with convulsions, stiff neck, bilateral Babinski signs, sluggish deep reflexes, Chaddock and Oppenheim signs, then absence of reflexes; temperature 105 F. Improvement after 5 days	Faintly pink; lymphocytes 30 per cu. mm.; polymorphonuclear leukocytes 8 per cu. mm.; total protein 79 mg. per 100 cc.; sugar 82 mg. per 100 cc.; chloride 655 mg. per 100 cc.; colloidal gold curve 0012321000	Headaches twice a month; knee and ankle jerks more active on left than on right; child of average intelligence
32	13	F	1937	Brain tumor suspected; encephalomyelitis ?	Postrubella encephalitis	Rash for 3 days, disappearing 2 days before first convulsion. Right hemiparesis; right knee jerk more active than left; neck rigid; positive Kernig sign; another convulsion 10 days later	Initial pressure 180 mm. of water; clear; lymphocytes 2 per cu. mm.; total protein 85 to 35 mg. per 100 cc.; sugar 61 mg. per 100 cc.; chloride 728 mg. per 100 cc.; colloidal gold curve 1112221000	Patient well, frequently tired, sleeps a great deal; nystagmus; ankle jerk stronger on left than on right; slight finger tremor
95	5	M	1935	Postrubella encephalitis	Postrubella encephalitis	Rubella rash 3 days before onset; onset with right jacksonian convulsion; another convulsion next day; 2 convulsions on following day. Stupor, deviation of eyes, right hemiplegia, absence of knee jerks and right abdominal reflexes	Initial pressure 85 mm. of water; total protein 35 mg. per 100 cc.; lymphocytes 50 to 2 per cu. mm. (within eleven days); sugar 50 mg. per 100 cc.; chloride 720 mg. per 100 cc.; colloidal gold curve 0121100000	Complete recovery after 2 weeks; well now

TABLE 10.—*Case of Toxic Encephalitis Following Acute Enteritis, with Autopsy Record*

Case	Age	Sex	Year	Clinical Diagnosis	Autopsy Observations	Signs and Course	Spinal Fluid
50	10	F	1933	Bronchopneumonia; acute encephalitis?	Acute colitis, gastrointestinal hemorrhages, hypertrophy of mesenteric nodes, bronchopneumonia. Cerebral vessels congested, small perivascular hemorrhages in the thalamus, thrombi(?); few small additional hemorrhages in brain substance. Diagnosis: encephalitis after acute enteritis	Marked abdominal pain of 1 day's duration, followed by headaches and coma; positive Kernig sign, with some rigidity of neck; temperature 106 F. Died after 2 days	Clear; polymorphonuclear leukocytes 3 per cu. mm.; lymphocytes 8 per cu. mm.

TABLE 11.—*Miscellaneous Postinfectious Encephalitis; Recoveries*

Case	Age	Sex	Year	Clinical Diagnosis	Final Diagnosis	Signs and Course	Spinal Fluid	End Result
81	6	F	1928	Encephalitis lethargica	Postmumps encephalitis	One week before admission mumps on left side; 2 days afterward vomiting and dizziness. Coma on admission; talked incoherently; condition cleared up within a few days; pupils dilated, reacted insufficiently to light; no signs of meningeal irritation	Initial pressure increased; clear; lymphocytes 1 per cu. mm.; polymorphonuclear leukocytes 2 per cu. mm.; normal protein	On discharge ten days later somewhat dull, otherwise normal
31	60	F	1928	Encephalitis	Toxic encephalitis during erysipelas	Patient semicomatose; slight rigidity of neck; erysipelas cleared up 2 weeks later	Cells 13 per cu. mm.; colloidal gold curve 0100000000	Well; no neurologic signs

TABLE 12.—*Encephalitis and Encephalomyelitis After Vaccination; Recoveries*

Case	Age	Sex	Year	Clinical Diagnosis	Final Diagnosis	Signs and Course	Spinal Fluid	End Result
10	39	F	1934	Encephalomyelitis after antirabic inoculation	Encephalomyelitis after antirabic inoculation	Two days after last of 14 intramuscular antirabic injections pain in epigastrium; loss of control of legs; nystagmus, patellar and ankle clonus bilaterally; Chaddock and Babinski signs; improvement after 4 days	Initial pressure 120 mm. of water; clear; lymphocytes 6 per cu. mm.; total protein 30 mg. per 100 cc.; colloidal gold curve 0123211000 (eight days after onset)	Burning feeling in chest, like a girdle; occasional headaches; lower part of legs frequently numb; nystagmus; reflexes of right arm stronger than of left; slight intention tremor present on right side (?); Oppenheim sign on left
64	5	F	1928	Encephalitis	Postvaccinal encephalitis	Five days before admission vaccination against smallpox; convulsions on admission; 4 years before bilateral otitis with hemiplegia on the right; still drags leg	Increased pressure, cells and globulin increased	Discharged as well after 10 days
78	55	M	1936	Pernicious anemia; postvaccinal encephalitis	Pernicious anemia; postvaccinal encephalitis	Thirteen days before admission vaccination against smallpox; disorientation; confusion; abdominal pain; no neurologic abnormalities	Initial pressure normal; total protein normal; cells 8,000 per cu. mm.; two weeks later 8 cells per cu. mm.; normal sugar and chloride content	After 2 weeks no signs of encephalitis

Comment.—It is questionable why "toxic" encephalitis is present in some cases of postinfectious nervous complications and "proliferative" encephalitis in others. Ferraro and Scheffer [9] contended that it depends on the power of the toxic factor. Rapid death or complete recovery after a few days may, however, occur in either group.

It is obvious from the cases reported and from others in the literature that a tendency to produce encephalitis or encephalomyelitis is by no means confined to the "virus" diseases, such as vaccinia and measles. In the series reported here, the largest group of cases of postinfectious encephalitides followed pneumonia.

Cultures of the spinal fluid and nerve tissues were, of course, sterile in all cases in this group. The cases in which cultures showed evidence of infection of the nervous system were placed in the category of "infectious encephalitis."

It is perhaps a natural assumption that the cerebral lesions of the postinfectious encephalitides are the result of invasion of the nerve tissue by the original infectious agent. It is obvious that many of the observations already presented—the uniformity of the lesions, their presence in sterile brain substance and the lack of suppuration—are against such an assumption. Putnam [3] and Putnam and Alexander [6] have produced evidence that the thromboses, which are so commonly associated with the proliferative encephalitis, are primary to the parenchymal changes.

UNCLASSIFIED ENCEPHALITIDES

In 2 cases (table 13) the diagnosis of encephalitis or encephalomyelitis was definite, in view of the neurologic signs and the increase of total protein and cells in the spinal fluid. It should be noted that both the patients were young. The spinal fluid could not be differentiated from that of patients with postinfectious encephalitis or encephalomyelitis. Also, the course and recovery were as rapid as they are in many cases of acute infection. It should be mentioned that occasionally during an epidemic of exanthematous disease some exposed children have been described as presenting encephalitis and encephalomyelitis without the exanthema having been noted. Similar instances have been described during epidemics of mumps in patients without any swelling of the parotid gland.[17] Perhaps this was the course of events in the 2 aforementioned cases. Multiple sclerosis should also be considered. Though there was a history of trauma in both cases, the changes in the spinal fluid were those of an exudative disease and not of traumatic encephalitis. Epileptic seizures persisted in both cases.

17. Putnam, J. J.: The Relation of Infectious Processes to Diseases of the Nervous System, Am. J. M. Sc. **109**:254, 1895. Birnberg, T. L.: Mumps Meningo-Encephalitis, Minnesota Med. **22**:173, 1939.

TABLE 13.—*Unclassified Encephalitis and Encephalomyelitis*

Case	Age	Sex	Year	Clinical Diagnosis	Final Diagnosis	Signs and Course	Spinal Fluid	End Result
90	13	M	1937	Encephalomyelitis, cause unknown	Postinfectious encephalitis ?	Seizures, Kernig sign, Babinski and Chaddock signs bilaterally; strabismus; head trauma 7 days previously	Clear; Pandy reaction increased; total protein 135 to 109 mg. per 100 cc.; cells 771 to 62 per cu. mm.; 73 per cent polymorphonuclear leukocytes; sugar 64 to 119 mg. per 100 cc.; chloride 676 per 100 cc.	Seizures; patient otherwise well
16	15	M	1938	Encephalitis, cause unknown	Postinfectious encephalitis ?	Had head trauma 5 months previously; onset with attacks of loss of sensation on right side and loss of consciousness; pyramidal signs on right; first symptom, sudden numbness of right hand	Initial pressure 170 to 120 mm. of water; cloudy, with shreds; cells up to 11,000 per cu. mm.; 88 per cent polymorphonuclear leukocytes; total protein 74 to 22 mg. per 100 cc.; sugar and chloride contents normal	Had 1 other convulsion; patient otherwise well; right pupil smaller than left; right reflexes hyperactive

CASES IN WHICH MULTIPLE SCLEROSIS DEVELOPED

The diagnosis of multiple sclerosis (table 14) is based chiefly on the typical course, with remissions, exacerbations and slow progression. It is interesting that in 4 of the 5 cases numbness was a prominent symptom at the beginning of the disease. While numbness is usually observed in cases of encephalomyelitis, it was not noted in the cases of postinfectious encephalitides in this series and may perhaps be taken as a characteristic of cases of encephalitis in which multiple sclerosis develops. The encephalitic lesions may be too small to cause sensory disturbances in cases of the postinfectious type, except when involving the spinal cord, as in encephalomyelitis. Another manifestation suggestive of multiple sclerosis is that the spinal fluid was normal in 3 of the 5 cases. Alteration in the cell count occurs in about 30 per cent and increase of total protein in 25 per cent of cases of multiple sclerosis.[18] In my experience, an abnormal spinal fluid prevails in cases of multiple sclerosis with the clinical picture of encephalomyelitis, which, as in case 92, closely resemble those of *neuromyélite optique aiguë*. Case 99 is of particular interest. The first attack began subacutely and, two months later, entered an acute stage after an influenza-like illness, with headaches, malaise and slight increase in temperature. A relapse occurred after an infection of the upper respiratory tract. The clinical picture, as well as the absence of changes in the spinal fluid, suggested strongly that the patient was suffering from multiple sclerosis. Unlike the patients suffering from encephalitis after infections of the upper respiratory tract, who did not have relapses and either recovered or died within a few days, this patient stayed in the hospital four months on his first admission and five weeks on his second and had, even during his remission, marked difficulties in locomotion. In some cases the clinical differentiation between acute encephalomyelitis and acute multiple sclerosis is perhaps arbitrary.

It has been shown by Putnam [19] that there is a close relation between various types of disseminated encephalomyelitides, including the postinfectious encephalitides and encephalomyelitides, and acute multiple sclerosis. A similar "encephalomyelitic reaction" [6] can be found in these diseases, which is characterized, among other features, by the occurrence of thrombosed vessels. Normal spinal fluid seems to point to the development of multiple sclerosis, that is, a tendency of the disease to recur.

18. Merritt, H. H., and Fremont-Smith, F.: The Cerebrospinal Fluid, Philadelphia, W. B. Saunders Company, 1937.

19. Putnam, T. J.: Studies in Multiple Sclerosis: VII. Similarity Between Some Forms of "Encephalomyelitis" and Multiple Sclerosis, Arch. Neurol. & Psychiat. **35**:1289 (June) 1936; Lesions of "Encephalomyelitis" and Multiple Sclerosis: Venous Thrombosis as the Primary Alteration, J. A. M. A. **108**:1447 (May 1) 1937.

TABLE 14.—*Cases in Which Multiple Sclerosis Developed*

Case	Age	Sex	Year	Clinical Diagnosis	Final Diagnosis	Signs and Course	Spinal Fluid	End Result
99	6	M	1932	Acute encephalitis; encephalomyelitis	Multiple sclerosis	Vomiting and dizzy spells 2 months before admission; within few days complete paralysis and numbness of both legs; nystagmus; Babinski sign; incontinence of urine; recovery within 3 weeks	Total protein 20, 45, 39 mg. per 100 cc.; lymphocytes 11, 7 per cu. mm.; sugar 80 mg. per 100 cc.; chloride 711 mg. per 100 cc.; colloidal gold curve 0111100000 Spinal fluid during relapse in 1939: Total protein 43 mg. per 100 cc.; lymphocytes 4 per cu. mm.; sugar 62 mg. per 100 cc.; chloride 73 mg. per 100 cc.; colloidal gold curve 0122110000	Weakness of legs persistent; in April 1939 an infection of the upper respiratory tract, with fever; after 2 weeks same neurologic picture as in 1932, with paraplegia of legs, nystagmus, Babinski sign, paresthesia of arms, respiratory difficulties; recovery within 20 days
92	15	F	1937	Acute optic neuritis; acute encephalomyelitis	Multiple sclerosis	Dysuria and frequency of urination; headaches, blurred vision, stiff neck, sleepiness, weakness and numbness of legs, blurred fundi, lesions of pyramidal tract	Initial pressure 220 mm. of water; slightly cloudy; lymphocytes 181 per cu. mm.; sugar 57 mg. per 100 cc.; chloride 714 mg. per 100 cc.; colloidal gold curve 00011110000	Markedly improved after 6 weeks; remissions and exacerbations
89	30	M	1930	Encephalitis ?	Multiple sclerosis	Numbness of legs, amblyopia, double vision	Normal	Varying course with remissions and exacerbations
15	40	F	1936	Multiple sclerosis (?); subacute encephalitis; tumor of brain suspected	Multiple sclerosis	Numbness and tingling of extremities, slurred speech, tremor of head, diplopia, intention tremor	Initial pressure 115 mm. of water; clear; total protein 18 mg. per 100 cc.; lymphocytes 4 per cu. mm.; colloidal gold curve 0100000000	Nystagmus, intention tremor and absence of abdominal reflexes; Oppenheim sign on right; patient tired, otherwise well
26	28	M	1938	Acute encephalomyelitis, cause unknown; multiple sclerosis ?	Multiple sclerosis	Inability to void, headache, weakness of legs, blurred vision, hyperesthesia; discharged much improved	Initial pressure 140 mm. of water; clear; total protein 24 mg. per 100 cc.; lymphocytes 2 per cu. mm.; colloidal gold curve 0010000000	Tingling and numbness of both hands; Horner syndrome on right; change in abdominal reflexes and reflexes of legs; patient otherwise well

DIFFUSE PERIAXIAL ENCEPHALITIS

The diagnosis in the 2 cases, 1 of an adult and 1 of a child, is based on blindness, signs of injury to the pyramidal tract, somnolence, remissions and exacerbations. The spinal fluid showed nothing characteristic. The adult had a marked increase of protein in the spinal fluid, while the child's fluid was normal.

TOXIC ENCEPHALITIS CAUSED BY EXOGENOUS POISONS

In 4 cases of this type the condition was caused by alcohol, in 2 by arsenic, in 1 by salicylic acid and in 1 by lead. Though damage to the brain might perhaps be caused by any chemical taken in excessive amounts, it is most frequently observed in cases of chronic alcoholism. Evidence has, however, been accumulated within the last years which shows that a deficiency in nutrition, chiefly of vitamins, is largely responsible for the nervous complications of chronic alcoholism.

The clinical and pathologic entity "encephalitis haemorrhagica superior" was first described by Wernicke, and the disease has been given his name. In this, as in toxic encephalitides, infiltrations are absent. The microscopic picture is dominated by hemorrhages, hyperemia and occasional new formation of capillaries. It should be noted that in Wernicke's polioencephalitis, the severest lesions being in the mesencephalon and diencephalon, the clinical picture is characterized by disturbances of the oculomotor nerves and frequently by nystagmus. In cases of poisoning due to most other chemicals the lesions are more diffuse. In only a few of these cases are the neurologic lesions characterized by hyperemia and hemorrhages. In others, for instance, those of intoxication by carbon monoxide or nitrobenzene, the neuropathologic picture is that of localized softenings, partly or entirely caused by failure of blood supply.

INFECTIOUS ENCEPHALITIDES

Encephalitis After Otitis Media or Mastoiditis.—The pathologic picture may be that of localized encephalitis extending from the meningeal exudate or abscess into the brain substance. It is known that frequently meningeal signs dominate the clinical picture. These may, in cases in which the picture is complicated by suppurative encephalitis, be accompanied by various additional neurologic signs. The spinal fluid in such cases is purulent. This was the entity found in the 2 cases in which death occurred. But, as has been pointed out by many otologists and has been proved by Grinker,[1] among others, there may be associated with otitis media or mastoiditis encephalitis characterized chiefly by hyperemia, new formation of capillaries and some cell damage—a picture belonging to the group of toxic postinfectious encephalitides. Infiltrations are absent in these cases, and the spinal fluid is normal or has a moderate increase in cells. On the other hand, cases have been

reported, mostly among children,[20] in which the clinical picture and spinal fluid findings were identical with those in cases of abscess of the brain. However, no pus could be found on exploration, and recovery resulted. The third case reported, that of an infant aged 1 year, apparently belongs in the latter group. On admission both ears were discharging, and the child had generalized convulsions. After these symptoms had subsided, right hemiplegia was noted. The spinal fluid, taken sixteen days after the onset of the convulsions, was clear and contained 40 cells, chiefly polymorphonuclear leukocytes, per cubic millimeter; 24 mg. of total protein and 40 mg. of sugar per hundred cubic centimeters. When the patient was discharged the hemiplegia was improving. The fact that the spinal fluid was examined late in the course of the disease renders the classification of this case even more difficult. At present, it remains an open question whether cases of this type belong to the group of infectious or postinfectious encephalitides.

Suppurative Encephalitis After Fracture of the Skull.—All 3 patients in this group died. All had extreme changes in the spinal fluid, with the total protein increased to 2,400 mg. per hundred cubic centimeters, more than 12,000 polymorphonuclear cells per cubic millimeter and an initial pressure of around 400 mm. of water. The neuropathologic picture was that of suppurative encephalitis. The presence of signs of an intracerebral lesion together with inflammatory changes in the spinal fluid justifies the diagnosis of encephalitis.

Miscellaneous Cases of Infectious Encephalitis.—The diagnoses of pneumococcic encephalitis and meningitis were confirmed at autopsy and by culture of the spinal fluid and nerve tissue in the case of 2 infants. In each case the spinal fluid was purulent, with a marked increase of leukocytes. The spinal fluid in a case of encephalitis due to Trichina, three weeks after the onset of the disease, was normal. Four years afterward the patient still had nystagmus, a Babinski sign on the left and slight alterations in the deep reflexes. The spinal fluid in the case of typhus fever encephalitis was xanthochromic, with 60 lymphocytes per cubic millimeter and 68 mg. of total protein per hundred cubic centimeters. Except for impairment of pupillary reactions, the patient has recovered completely.

The development of encephalitis in persons with tuberculosis has been reported and discussed by Oppenheim [21] and by Weil.[22] A case

20. Adson, A. W.: Pseudo-Brain Abscess, S. Clin. North America **4**:503, 1924. Symonds, C. P.: Localized Non-Suppurative Encephalitis, Proc. Roy. Soc. Med. (Sect. Otol.) **20**:1142, 1927. Atkinson, M.: Localized Nonsuppurative Encephalitis Adjacent to a Focus of Infection in the Skull, Arch. Neurol. & Psychiat. **41**:446 (March) 1939.

21. Oppenheim, H.: Lehrbuch der Nervenkrankheiten, Berlin, S. Karger, 1923, p. 1292.

22. Weil, A.: A Text-Book of Neuropathology, Philadelphia, Lea & Febiger, 1933.

of a patient with active tuberculosis apparently belongs to this group of encephalitides. He had a sudden attack of headaches, diplopia, blurred vision and stiffness of the neck; speech was slurred, and he was apathetic. The spinal fluid showed normal protein content and an increase of leukocytes to 230 per cubic millimeter. After a few days the cell count returned to normal, and the patient was discharged as much improved. Further observations are necessary to clarify this syndrome. It may belong to the infectious or postinfectious group or may represent a deficiency syndrome, as the "tuberculous" neuritides probably do.

PRIMARY INFECTION OF THE CENTRAL NERVOUS SYSTEM (PORTAL OF ENTRANCE UNKNOWN)

Lethargic Encephalitis.—In the 2 cases (table 15), in which the disease began during 1928 and 1930, parkinsonism developed. In case 28, occurring in 1933, almost complete recovery has taken place. This case is different from the 2 others also on account of the marked changes in the spinal fluid, which occur comparatively rarely in lethargic encephalitis. Although in this case the pupillary changes and the mental picture are strongly suggestive of lethargic encephalitis, another agent, for instance, an infection of the respiratory tract, may have brought about the encephalitis; the diagnosis of lethargic encephalitis is therefore suggestive, but not certain. The 1 patient who died showed a typical clinical nature. Problems of etiology, epidemiology and treatment of lethargic encephalitis are summarized in the reports of the Matheson Commission.[22a]

POST-TRAUMATIC NONSUPPURATIVE ENCEPHALITIS

It is known that the neuropathologic picture in post-traumatic encephalitis (table 16) is that of multiple small hemorrhages and softenings in the brain substance. Frequently, as in my 2 cases, the encephalitis is rather localized. There may be an increase in protein of short duration in the spinal fluid, or, as in case 5, the spinal fluid may be bloody. Changes in reflexes may persist, even when there is no subjective impairment of health. Among other features, the course differentiates the syndrome from subdural hematoma. If the patient survives, improvement occurs rather rapidly.

CASES IN WHICH A DIAGNOSIS OF ENCEPHALITIS WAS OBVIOUSLY ERRONEOUS

Benign Lymphocytic Meningitis.—The clinical picture and laboratory findings in cases of benign lymphocytic meningitis, a condition

22a. Epidemic Encephalitis, Second Report by the Matheson Commission, New York, Columbia University Press, 1932.

TABLE 15.—*Primary Infections of the Central Nervous System (Portal of Entrance Unknown)*

Case	Age	Sex	Year	Clinical Diagnosis	Final Diagnosis	Signs and Course	Spinal Fluid	End Result
8	13	M	1929	Acute lethargic encephalitis	Acute lethargic encephalitis	Diplopia, drowsiness, sleepiness, jerking of left leg, slight fever	Initial pressure 150 mm. of water; total protein 25 mg. per 100 cc.; cells 0; colloidal gold curve 1122100000	Two months later parkinsonism developed, which is marked and typical now
23	10	F	1930	Encephalitis	Lethargic encephalitis	Temperature 100 F., headaches, vomiting, semicoma, stiff neck; strabismus	Total protein 33 mg. per 100 cc.; sugar 59 mg. per 100 cc.; colloidal gold curve 0122210000	Parkinsonism of moderate degree; masklike face; slowness of movements; impairment of convergence; changes in reflexes
28	33	F	1933	Lethargic encephalitis	Lethargic encephalitis	Temperature 99 F., sudden confusion; irrational; sluggish pupillary reaction to light	Initial pressure 120 mm. of water; clear; total protein 65, 29 mg. per 100 cc.; cells 170, 10 per cu. mm.; 8% polymorphonuclear leukocytes; chloride 760 mg. per 100 cc.; sugar 47, 68 mg. per 100 cc.; colloidal gold curve 1121110000	Ataxia; ankle jerk less active on left than on right
57	32	F	1928	Lethargic encephalitis	Lethargic encephalitis	Headaches and drowsiness (severe headaches for 2 months), jerking of eye, numbness of hands; slept much for 4 weeks; saw double; pupils irregular; Babinski sign on left	Initial pressure 150 mm. of water; total protein 33 mg. per 100 cc.; lymphocytes 5 per cu. mm.; chloride 726 mg. per 100 cc.	Death; no autopsy

TABLE 16.—*Post-Traumatic Nonsuppurative Encephalitis*

Case	Age	Sex	Year	Clinical Diagnosis	Final Diagnosis	Signs and Course	Spinal Fluid	End Result
5	13	M	1937	Acute encephalitis, cause unknown	Condition after head trauma	Two days before admission trauma to head, followed by headaches, dizziness, difficulty in vision; visual and acoustic hallucinations; restraints necessary; fundi irregular; nystagmus; sluggish ankle jerks; Babinski, Chaddock, Gordon, Rossolimo and Oppenheim signs	Initial pressure 150 mm. of water; blood tinged	Patient well; ankle jerk more active on right than on left; no Babinski sign; no nystagmus
30	6	M	1934	Acute encephalitis	Condition after head trauma	Three days before onset head trauma; convulsions; right arm paralyzed; could not talk for 4 days or read afterward	Total protein 55, 34 mg. per 100 cc.; polymorphonuclear leukocytes 4 per cu. mm.; lymphocytes 1 per cu. mm.; sugar and chloride content normal	Patient well; temper tantrums; right arm slightly weaker than left; reflexes of right arm weaker than those of left

bearing many additional names, such as epidemic serous meningitis and aseptic lymphocytic meningitis, have been elaborated within the last year.[23] Since 1934 there has been no additional case in which a revision warranted changing the original diagnosis of "encephalitis" to that of benign lymphocytic meningitis. It should be noted that in 4 of the 6 cases reported here there was a definite infection of the upper respiratory tract before the onset of the disease. Nevertheless, the syndrome of severe headache, stiff neck, malaise and occasional dizziness, associated with marked increase in the number of lymphocytes in the spinal fluid, only mild increase in the total protein of the fluid and absence of any severe localizing neurologic signs, differentiates this disease from encephalitis after infection of the upper respiratory tract. The end results are excellent, unlike those of encephalitis after infection of the upper respiratory tract. The patients reported on recovered completely within a few days, though a course of as long as two weeks has occasionally been reported. No complement fixation tests were performed in any of these cases.

Infectious and Postinfectious Conditions Other than Encephalitis.—The diagnosis of encephalomyelitis was made in 3 cases of polyneuritis in which the spinal fluid showed no increase in cells but an increase in total protein, a typical finding in certain cases of polyneuritis. One of the 3 patients became sick after an infection of the upper respiratory tract; the other 2, after scarlet fever and serum sickness, respectively. The occurrence of neuritis and polyneuritis after injection of serum has been reported.[24] The onset of encephalomyelitis may, of course, be masked by flaccid paralysis.

The laboratory and autopsy observations and clinical signs led to the diagnosis of meningococcic, pneumococcic or syphilitic meningitis in 4 cases of fatal termination.

In 1 case, the absence of knee jerks, the spinal fluid findings (increase of cells with normal protein content) and the course of the disease made a diagnosis of abortive poliomyelitis more likely than that of encephalitis. Both diagnoses were suggested while the patient was in the hospital.

The diagnosis of postmumps encephalitis was made in 2 cases and of lethargic encephalitis in 1 case; the patients had had mumps one, two and three weeks, respectively, before the onset. The spinal fluid

23. Rivers, T. M., and Scott, T. F. M.: Meningitis in Man Caused by a Filtrable Virus, J. Exper. Med. **63**:415, 1936. Viets, H. R., and Warren, S.: Acute Lymphocytic Meningitis, J. A. M. A. **108**:357 (Jan. 30) 1937.

24. Kennedy, R. F.: Certain Nervous Complications Following the Use of Therapeutic and Prophylactic Sera, Am. J. M. Sc. **117**:555, 1929. Gordon, A.: Motor Paralysis of Individual Nerves Following Administration of Prophylactic Serums, J. A. M. A. **98**:1625 (May 7) 1932.

had an increase of cells, up to 500 per cubic millimeter, with normal protein content. Meningeal signs were pronounced. No signs of intracranial lesions were found, and on retrospect, therefore, the most appropriate diagnosis in all 3 cases seems to be postmumps meningitis, rather than encephalitis. The patients recovered completely, although 2 had been in coma.

A youth aged 17 had septicemia resulting from multiple cutaneous abscesses. Shortly before his death he had almost complete left hemiplegia. The spinal fluid was normal. The diagnosis was septicemia and toxic encephalitis. Experience has shown that in such cases the pathologic change is septic thrombosis of cerebral vessels rather than toxic encephalitis.

A man aged 73 had had paralysis of the seventh nerve of a few weeks' duration, together with herpetic lesions over the trigeminal nerve. The spinal fluid contained 14 lymphocytes and 2 polymorphonuclear cells per cubic millimeter, but examination otherwise gave normal results. The patient recovered completely. "Acute encephalitis" was originally suggested. Lesions of the cranial nerves may occur during the course of herpes zoster of the trigeminal nerve, and cases have been reported frequently. Postmortem observations are available in 1 case of herpes zoster encephalomyelitis.[25] In this patient the only sign of cerebral involvement was delirium of a few days' duration.

Miscellaneous Disorders.—Tremor, vomiting and headaches induced the suspicion of encephalitis, of unknown origin, in 2 cases in which, on reexamination, the patients proved to be heavy drinkers, with all the signs of chronic alcoholism. Drowsiness, visual difficulties and confusion in 1 case and tremor and anesthesia in another gave rise to a suspicion of encephalitis, which proved on reexamination to be hysteria. Vomiting, fainting and nystagmus, of one day's duration, induced the diagnosis of encephalitis in 1 case, in which reexamination revealed food poisoning as the cause of the condition. In these 5 cases the spinal fluid was normal. It seems justifiable to question the diagnosis of "encephalitis" in cases in which the spinal fluid is normal and the clinical picture gives no evidence of the presence of epidemic encephalitis or toxic encephalitis caused by infectious or exogenous poisons.

Chronic degenerative disease of the brain was misleading in 2 cases. The long-drawn course, with epileptic seizures, progressive mental deterioration and gradual increase of neurologic signs, especially of pyramidal disturbance, observed in a child, with a syndrome first diagnosed as lethargic encephalitis and nine years later as tuberous sclerosis is not found in any case of the former disease.

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25. Thalhimer, W.: Herpes Zoster: Central Nervous System Lesions Similar to Those of Epidemic (Lethargic) Encephalitis, Arch. Neurol. & Psychiat. **12**: 73 (July) 1924.

In the second case, that of a man, the condition started with sudden convulsions and passed into status epilepticus, with death two days after the onset. The original diagnosis was encephalitis. Autopsy revealed atypical myelin formation in the globus pallidus on each side.

Two additional patients, aged 17 and 4 years, respectively, died in status epilepticus, of sudden onset. This was preceded by anorexia of two days' duration in the Negro, aged 17, while there were no premonitory signs in the child. The spinal fluid showed an increase in cells and a normal protein content in both cases. Autopsy observations were those typical of status epilepticus. There was generalized edema of the central nervous system. Slight hyperemia was present only in the spinal cord of the older patient. There was no preceding infection.

Headache of many months' duration, increase in the initial lumbar spinal fluid pressure to 300 mm., gradual increase of neurologic signs, all of which were found in a woman aged 45, represent a syndrome typical of tumor of the brain, not of encephalitis. Both conditions were suggested in the clinical diagnosis in this case.

Unconsciousness was the only symptom that led to the diagnosis of "acute encephalitis" in a child aged 6 years. This was caused, as shown by the observations at autopsy, by a disease not primarily affecting the brain. Postmortem examination revealed lobar pneumonia and fibrinous pericarditis.

CASES IN WHICH DIAGNOSIS WAS NOT CLEAR

In 6 cases the history and the neurologic and laboratory findings did not suffice for a definite diagnosis of encephalitis. Four of the patients died a few hours after admission to the hospital. They had been admitted in a comatose condition. No autopsy was performed in 3 cases. In the fourth, the case of a woman aged 55 with alcoholism, the changes noted at autopsy were "hemorrhage and softening of the corpus callosum." She had been admitted with slow, athetoid movements of the hands, a Babinski sign bilaterally and rigidity of the neck. The spinal fluid contained 105 mg. of total protein per hundred cubic centimeters, without increase in cells. The clinical diagnosis was encephalitis, of unknown origin. No microscopic slides were available, and therefore no definite statement can be made about the origin of the lesion.

In the fifth case infantile encephalitis of long standing was suggested by displacement of the ventricular system. In the last case the patient had a multitude of diseases, among them pneumonia and uremia, which complicated the picture. He could not be reached for reexamination.

COMMENT

Quantitative and morphologic examinations of blood did not show changes specific for the different groups. The blood picture was usually

that of the underlying disease in cases in which the encephalitis was secondary. There was a moderate increase of leukocytes in all cases of the postinfectious encephalitides. This was true also in the 2 unclassified cases (cases 16 and 90), in which no preceding or accompanying infection could be proved. The white cell counts increased to 13,000 and 14,000 per cubic millimeter, respectively, for a few days. The differential count and sedimentation rates were normal. An increase of leukocytes was present also in cases of encephalitides following infections in which leukopenia usually occurs. This was found in the 3 cases of postrubella encephalitis. In 1 of them (case 32) the white cell count was 21,000 per cubic millimeter.

Epileptic seizures persisted in 3 children who had had encephalitis. One was a boy aged 5 years, who had encephalitis after an infection of the upper respiratory tract (case 13); the other 2 had unclassified conditions (cases 16 and 90). In each case the seizures had started during the acute phase and had then continued.

Finally, it should be especially emphasized that none of the patients presented a syndrome wholly typical of the St. Louis encephalitis of 1933.[26] In 1 patient (case 44) microscopic changes were different from those usually seen in postinfectious encephalitis and were suggestive of a sporadic incidence of equine encephalomyelitis. No attempt to identify the virus was made in this patient.[27]

SUMMARY

The diagnosis of acute encephalitis or encephalomyelitis was made in 100 cases at the Boston City Hospital within and including the years 1929 and 1938. In 37 of these cases there was a fatal outcome. Autopsy observations were available in 19 of the 37 cases. In 50 of the remaining 63 cases reexamination during 1938 and 1939 was possible. The diagnosis had to be revised in 30 of the 100 cases.

A survey was made of the signs, symptoms, laboratory findings, especially in the spinal fluid, observations at autopsy, residuals and end results in the various cases. A numerical account of the different groups is given in tables, and typical features are discussed.

In cases of postinfectious encephalitides two entities can be recognized on the basis of clinical and pathologic evidence. In the first group signs of diffuse cerebral involvement are presented, such as headaches, vomiting, muscle twitchings, stiffness of the neck and, in children, frequently generalized convulsions. The spinal fluid is normal, with occasional moderate increase of the white cell count. In these cases the histologic changes are those of "toxic" encephalitis, characterized by

26. Report on the St. Louis Outbreak of Encephalitis, Public Health Bulletin 214, United States Treasury Department, Public Health Service, 1935.

27. Feemster, R. F.: Outbreak of Encephalitis in Man Due to Eastern Virus of Equine Encephalomyelitis, Am. J. Pub. Health **28**:1403, 1938.

hyperemia, perivascular hemorrhages, new formation of capillaries and cell damage, but absence of infiltration and demyelination.

In the second group signs of localized neurologic lesions, such as palsies of the cranial nerves (from nuclear or root lesions), pyramidal tract involvement, expressed by paralyses of limbs and the Babinski sign, are presented. In these cases there is an increase of total protein and of cells in the spinal fluid, which as a rule disappears or diminishes within a few days. The neuropathologic features are cellular infiltrations, which are frequently located around vessels, and occasionally demyelination. Thrombosed vessels are frequently seen in the acute stage. Hemorrhage may or may not be present. "Proliferative" encephalitis or encephalomyelitis appears to be a proper designation for this group.

Most encephalitides caused by exogenous poisons belong clinically and pathologically to the toxic encephalitis group. But this entity can also be found in cases of various postinfectious encephalitides. This has been proved at autopsy in some cases of pneumonia, while in others the condition belonged to the group of proliferative encephalitides and encephalomyelitides. Evidence is found in the literature that either entity may occur in various postinfectious conditions, such as those following measles, vaccination, mumps and rubella.

Cases of apparent "encephalitis," with signs of localized neurologic lesions and normal spinal fluid, are suggestive of multiple sclerosis, provided lethargic encephalitis can be ruled out.

No condition wholly typical of the St. Louis encephalitis was found among our patients. In 1 case the clinical and microscopic picture could hardly be differentiated from that of equine encephalomyelitis in man.

Of the 30 cases in which the clinical diagnosis had to be revised at autopsy or reexamination, the largest group consisted of 6 cases of benign lymphocytic meningitis, a syndrome which before 1934 was not well recognized.

Examination of the blood in cases of encephalitides and encephalomyelitides revealed moderate leukocytosis, without typical differential count.

Epileptic seizures persisted as residuals in 3 children.

DISCUSSION

Dr. Bronson Crothers: I wonder if Dr. Adler feels strongly about the use of the word "postinfectious." In a number of cases of this type the disease has its onset, coincidentally at least, with manifestations of the infection. I think that "postinfectious" rather than "infectious" is confusing to some.

Dr. Alexandra Adler: When I made this survey, I noticed that there was some confusion in the use of this term. From the practical point of view it seems best to designate the encephalitis in cases in which bacteria can be identified as "infectious encephalitis." I use the term "postmeasles" encephalitis even when the cerebral condition occurs before the onset of measles.

COMPARATIVE STUDY OF METRAZOL TREATMENT AND CONTROL OBSERVATIONS OF SCHIZOPHRENIA

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The convulsive treatment of schizophrenia introduced by Meduna aroused great interest, and numerous reports have appeared in the literature.

Meduna [1] originally claimed 99.6 per cent of remissions in cases of psychosis of less than six months' duration, 84 per cent in those of eighteen months' duration and 64.28 per cent in those of less than five years' duration. Sorger and Hofmann [2] obtained remissions in 76.3 per cent of cases of psychosis of six months' duration, in 53.8 per cent of cases of psychosis of not more than one year's duration and in 26.5 per cent of cases of psychosis of over one year's duration. Scheuhammer and Wissgott [3] reported remissions in 69 per cent of cases of illness for one and one-half years or less. Friedman [4] claimed "definitely remissive changes" in 31 (77.5 per cent) of 40 cases of psychosis which had lasted from a month to twenty years. Meier [5] reported complete remissions in 5 cases, good remissions in 4 cases

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From the Hudson River State Hospital.

1. von Meduna, L.: Die Konvulsionstherapie der Schizophrenie, Psychiat.-neurol. Wchnschr. **37**:317 (July 6) 1935; Die Konvulsionstherapie der Schizophrenie, Halle, Carl Marhold, 1937.

2. Sorger, E., and Hofmann, E.: Beobachtungen und Ergebnisse bei der Cardiazol-Krampfbehandlung der Schizophrenie, Psychiat.-neurol. Wchnschr. **39**: 462 (Oct. 9) 1937.

3. Scheuhammer, P., and Wissgott, L.: Erfahrungen mit der Cardiazolbehandlung der Schizophrenie, Psychiat.-neurol. Wchnschr. **39**:286 (June 26) 1937.

4. Friedman, E.: Irritative Therapy of Schizophrenia: Practical Application and Theoretical Considerations, New York State J. Med. **37**:1813 (Nov. 1) 1937.

5. Meier, W.: Klinische Erfahrungen an 50 mit der Konvulsionstherapie nach L. von Meduna behandelten Schizophrenen, Schweiz. Arch. f. Neurol. u. Psychiat. **41**:100, 1938.

and lack of improvement in 1 case of psychosis of six months' duration. Of 7 other cases of psychosis of from one-half to one and one-half years' duration, there were a good remission in 1 and improvement in 3, and in the remaining 3 cases the patients failed to show any improvement. In a third group of 27 cases of chronic psychosis lasting more than one and one-half years there were a good remission in 1 case, improvement in 5 cases and failure to respond to the treatment in 21 cases. In a fourth group of 6 cases of chronic psychosis with an episodic course there were good remissions in 3 and improvement in 3 cases. Low and his associates [6] reported remissions in 66.7 per cent of cases of psychosis of from one to six months' duration and in 50 per cent of cases of psychosis of from six to twelve months' duration and recoveries in an average of 22.9 per cent of all cases of schizophrenia. Stähli and Briner [7] reported "social recovery" in 50 per cent of cases of psychosis of under one year's duration, in 13 per cent of cases of psychosis of one to five years' duration and in 5 per cent of cases of psychosis of over five years' duration. Ebaugh and Johnson [8] reported improvement "without any recurrence" in 62 per cent of cases in which treatment was completed. Delgado [9] obtained complete remissions in 7 cases and an incomplete remission in 1 case of psychosis of less than one and one-half years duration. Of 7 other cases in which the patients had been ill more than one and one-half years, there were complete remissions in 2, an incomplete remission in 1 and failure to improve in 4. Hahnemann [10] treated 207 patients and obtained full remissions in 40 and partial remissions in 69. Of 36 cases in which the psychosis had existed for less than one year, full remission was obtained in 25 (69 per cent), partial remission in 6 (17 per cent) and no improvement in 5 (14 per cent). Novotny [11] reported success in treatment in 74.07 per cent of cases of psychosis of less than one-half year's duration. Of the entire group there were full remissions in 21.67 per cent, good remissions in 19.17 per cent, partial remissions in 7.5 per cent, slight remission in 11.6 per cent, lack of improvement in 39.17 per cent and

6. Low, A. A.; Sonenthal, I. R.; Blaurock, M. F.; Kaplan, M.; Sherman I., and Whitcomb, F. C.: Metrazol Shock Treatment of "Functional Psychoses," Arch. Neurol. & Psychiat. **39**:717 (April) 1938.

7. Stähli, R., and Briner, O.: Beitrag zur Krampfbehandlung der Schizophrenie, Ztschr. f. d. ges. Neurol. u. Psychiat. **160**:649, 1938.

8. Ebaugh, F. G., and Johnson, G. S.: Status of Chemotherapy in Schizophrenic and Affective Reactions, Am. J. M. Sc. **197**:862 (June) 1939.

9. Delgado, H.: Treatment of Schizophrenia with Cardiazol in Convulsant Doses, J. Nerv. & Ment. Dis. **89**:625 (May) 1939.

10. Hahnemann, V.: One Year of Clinical Experiences in Treatment of Psychoses with So-Called Cardiazol Shock, Ugesk. f. læger **101**:771 (June 29) 1939.

11. Novotny, S.: Beitrag zur Cardiazoltherapie der Schizophrenie nach von Meduna (in Kombination mit der Schwefelfiebertherapie), Schweiz. Arch. f. Neurol. u. Psychiat. **43**:295, 1939.

a fatal termination in 0.83 per cent. Lehoczky and his associates[12] reported full remissions in only 21.6 per cent of patients ill less than six months and in 27.5 per cent of patients ill from six to twelve months. Reitmann,[13] in summarizing the results obtained with 840 patients suffering from "acute and subacute" schizophrenia treated in seven different countries, found complete remissions in 52 per cent. Meduna and Friedman[14] tabulated the results in the various clinics, both in Europe and in the United States, and summarized them thus:

> In the acute and subacute schizophrenic disorders (lasting less than one and one-half years) remissions were observed in 52 per cent of cases. According to the workers who further subdivided their cases into acute or early types (under six months' duration) the incidence in that group amounts to nearly 60 per cent . . .
>
> In chronic schizophrenia (lasting longer than from one to one and one-half years) there was a rate of remission of 10 per cent.

METHOD AND MATERIAL

In order to ascertain the value of the convulsive treatment of Meduna, we decided to observe simultaneously a control group. Because of the difficulty encountered in obtaining permission to treat patients with the acute form of the psychosis and because of spontaneous improvement of others while undergoing preliminary examinations, the disease in the great majority of cases in each group was of the chronic type. The usual technic was used. The initial dose was 4 cc. of a 10 per cent solution of metrazol. If there was no reaction the dose was gradually increased during subsequent treatments until a convulsion occurred. The control patients were given at the same time sterile physiologic solution of sodium chloride intramuscularly and were kept in bed in the same ward in which the patients were treated with metrazol.

This report is based on the results of treatment of 100 patients, 50 men and 50 women, and the results of observation of 71 control patients, 34 men and 37 women, and of 15 other patients, 12 men and 3 women, who recovered or improved while undergoing various tests and examinations. The duration of the psychosis was more than eighteen months in 78 per cent of patients in the treated group, in 84.5 per cent of patients in the control group and in only 13.4 per cent of patients in the group which improved spontaneously. The patients were followed for from six months to one year and a half after termination of treatment or control observation.

GENERAL SURVEY OF RESULTS

Of the 100 treated patients, 18 (18 per cent) showed various degrees of improvement (table 1). One man died of an abscess of the lung which developed after

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12. Lehoczky, T.; Eszenyi, M.; Horányi-Hechst, B., and Bak, R.: Katamnestische Untersuchung über die Insulin-Shock und Konvulsions-Therapie der Schizophrenie, Ztschr. f. d. ges. Neurol. u. Psychiat. **166**:24, 1939.

13. Reitmann, F.: Cardiazol Therapy of Schizophrenia: Some Statistical Data, Lancet **1**:439 (Feb. 25) 1939.

14. von Meduna, L., and Friedman, E.: The Convulsive-Irritative Therapy of the Psychoses, J. A. M. A. **112**:501 (Feb. 11) 1939.

the thirteenth convulsion. Eighty-one patients (81 per cent) failed to show any change in their mental condition. Of the patients who improved, 17 were released. Two (11.1 per cent) had relapses and were returned to the hospital.

Of the 71 control patients, 6 (8.4 per cent) showed various degrees of improvement and 65 (91.6 per cent) failed to improve. Five of the patients who improved were sent home. Two (33.3 per cent) had relapses and were returned to the hospital. On comparing the results in the two groups, one finds a much lower percentage of improvement in the control group.

Of the 15 patients who improved spontaneously 1 had a relapse while still in the hospital and 2 others have had relapses after their release.

TABLE 1.—*General Survey of Results*

	Treated Patients	Controls	Patients Who Improved Spontaneously
Improved	18 (18%)	6 (8.4%)	15 (100%)
Unimproved	81 (81%)	65 (91.6%)	0
Dead	1 (1%)	0 (0.0%)	0
Total	100 (100%)	71 (100%)	15 (100%)
Patients released	17	5	15
Number of relapses	2 (11.1%)	2 (33.3%)	3 (20.0%)

TABLE 2.—*Relation of Types of Results to Duration of Psychosis*

	Treated Patients				Controls				Patients Who Improved Spontaneously			
Duration of Psychosis	Recovered	Much Improved	Improved	Unimproved	Recovered	Much Improved	Improved	Unimproved	Recovered	Much Improved	Improved	Unimproved
Less than 6 mo.	0	3	4	1	0	0	1	0	1	4	2	0
6 to 18 mo.	0	1	5	8	0	1	1	8	0	5	1	0
Over 18 mo.	0	1	4	73	0	1	2	57	0	0	2	0
Total	0	5	13	82	0	2	4	65	1	9	5	0

We shall not discuss in detail results on the basis of sex, except to state that the men showed a somewhat greater percentage of improvement in all groups.

RELATION OF RESULTS OF TREATMENT TO DURATION OF PSYCHOSIS

In our attempt to correlate the results of treatment or of control observation and the duration of psychosis the prevailing criteria for recovery, marked improvement and improvement were used (table 2). There were no recoveries among the 8 treated patients with a psychosis of less than six months' duration. Three patients (37.5 per cent) showed much improvement, 4 (50 per cent) improved and 1 (12.5 per cent) failed to improve. One of the patients who improved had a relapse.

Of the 14 patients who were ill for from six to eighteen months, none recovered, 1 (7.1 per cent) showed much improvement, 5 (35.7 per cent) improved and 8 (57.1 per cent) failed to improve. One of the patients who improved had a relapse.

Of the 78 patients who had been ill for over eighteen months, none recovered, 1 (1.3 per cent) showed much improvement, 4 (5.1 per cent) improved and 73 (93.6 per cent) failed to improve. Included in this group is the patient who died.

In the control group only 1 patient had a psychosis of less than six months' duration; he improved. Of 10 patients who had been ill for from six to eighteen months, none recovered, 1 (10 per cent) showed much improvement, another (10 per cent) improved and 8 (80 per cent) failed to improve. The patient who improved had a relapse.

Of 60 patients with a psychosis of over eighteen months' duration, none recovered, 1 (1.66 per cent) showed much improvement, 2 (3.3 per cent) improved and the condition of the other 57 patients (95.1 per cent) remained unchanged. The patient who showed much improvement later had a relapse.

In the group of 15 patients who improved spontaneously 7 had been ill for less than six months. One of them (14.3 per cent) recovered, 4 (57.1 per cent) showed much improvement and 2 (28.5 per cent) improved. One of the patients who improved had a relapse. Of 6 patients with a psychosis of from six to eighteen months' duration, none recovered, 5 (83 per cent) showed much improvement and 1 (17 per cent) improved. One of the patients who showed much improvement had a relapse. Two patients who had been ill for more than eighteen months improved; 1 of them later had a relapse.

In summary, it can be stated that both the treated and the control patients with a shorter duration of psychosis showed a higher percentage of various degrees of improvement, that no recoveries took place in either group, that the percentage of improvement among the treated patients was higher than that among the controls and that the results in the group who improved spontaneously were superior to those in the two other groups, from the standpoint not only of the frequency but also of the degree of improvement.

RELATION OF DURATION OF REMISSIONS TO DURATION OF PSYCHOSIS

The 2 treated patients who had a relapse remained in the community less than six months. One of the patients had had a psychosis of less than six months, and the other of less than eighteen months' duration.

The 2 control patients who had a relapse likewise were out of the hospital for less than six months. One had had a psychosis of less than eighteen months' and the other of more than eighteen months' duration.

The 3 patients who improved spontaneously and later had a relapse had remissions lasting slightly less than six months. One had had a psychosis for less than six months, the second for between six and eighteen months and the third for over eighteen months. The last patient had a relapse while still in the hospital.

There are 16 treated patients out of the hospital who still maintain various degrees of improvement. Of 6 of these patients with a psychosis of less than six months' duration, 2 have been out of the hospital over one year, 2 eleven months, 1 seven months and 1 six months. Of 5 patients with a psychosis of from six to eighteen months' duration, 2 have been out of the hospital nine months and 3 seven

months. Of 5 patients with a psychosis of over eighteen months' duration, 1 has been out more than a year, 1 nine months, 1 seven months and 2 six months.

Of the 4 control patients still in the community, 1 with a psychosis of more than six months' but of less than eighteen months' duration has been out of the hospital slightly over one year. Of the 3 other patients with a psychosis of over eighteen months' duration, 1 has been out nine months and 2 six months.

Of the 6 patients with a psychosis of less than six months' duration who improved spontaneously, 1 has been out one and one-half years, 3 eleven months and 2 nine months. Of the 5 patients with a psychosis of from six to eighteen months' duration, 3 have been out for periods of from one to one and a half years, 1 eleven months and 1 nine months.

One patient with a psychosis of over eighteen months' duration has been out eleven months.

On the basis of these figures it can be said that with few exceptions patients with a shorter duration of psychosis have longer remissions.

AGE

The average age for the group of treated men who improved was 26.7 years and for the group who did not improve it was 33.1 years (table 3). The

TABLE 3.—*Average Ages of Patients in Three Groups*

	Men		Women	
	Improved	Unimproved	Improved	Unimproved
Treated	26.7	33.1	27.8	35.6
Control	21.3	34.2	30.0	34.3
Spontaneously	31.1	....	30.0	....

average ages for the corresponding control groups were 21.3 and 34.2 years respectively. For the group of treated women who improved the average age was 27.8 years, and for the group who did not improve it was 35.6 years. The figures for the control group were 30 and 34.3 years respectively. In the group who spontaneously improved, the average age for the men was 30 and for the women 31. These figures show that the patients who improved both in the treated and in the control group were younger than the patients who did not improve, the difference in the treated group being 7 years for the men and 8 years for the women and in the control group 13 years for the men and 4 years for the women.

It can be said, then, that in the treated as well as in the control group, the patients, both men and women, who improved were younger than the patients who did not improve.

NUMBER OF TREATMENTS AND CONVULSIONS

With 4 exceptions, each patient had 20 generalized convulsions, in addition to a number of light attacks. We do not use the term grand mal attack, as the metrazol convulsion is somewhat different from that observed in cryptogenic epilepsy. The mild attacks, however, are not unlike petit mal seizures. Of the 4 patients who constituted the exceptions, all of whom were men, 1 had pneumonia after 18 treatments, during which he had 13 generalized and 4 petit mal attacks;

another patient died of an abscess of the lung which developed after 19 treatments, during which he had 13 generalized convulsions and 4 minor attacks; treatment of a third patient was discontinued after 18 injections of metrazol, during which he had 7 generalized and 4 mild attacks, because of fracture of the femur sustained during a convulsion; treatment of a fourth patient was discontinued after 31 administrations of metrazol, during which he had 15 generalized convulsions, because of an extreme fear reaction which made further therapy inadvisable.

The smallest number of treatments in the group of men who improved was 18, the largest 28 and the average 23.8; for the group who did not improve, the patient who died being omitted, the figures were 21, 34 and 26.4, respectively.

The smallest number of treatments in the group of women who improved was 22, the largest 27 and the average 25; for the group who did not improve the figures were 21, 33 and 25, respectively.

Mild attacks occurred in 80 per cent of the men who improved, with a total of from 1 to 5 seizures per patient. They occurred in 90 per cent of the men who did not improve, with a frequency of from 1 to 10. The mild attacks occurred in 83 per cent of the group of women who improved, with a frequency of from 1 to 3, and in 59 per cent of the group of women who did not improve, with a frequency of 1 to 5.

Most of the patients who benefited from the treatment began to show signs of improvement after about 10 convulsions. One patient showed improvement after an attack of pneumonia, which developed after the thirteenth generalized convulsion; however, he had a relapse later.

While about the same total amount of metrazol was administered to the patients who improved and to those who did not improve, there was a difference in the amount given to the men and to the women. The average single dose for the women was 7 cc., and the average total dose for the course of treatment was 155.8 cc.; the average single dose for the men was 9.1 cc., and the average aggregate dose was 187.7 cc. These figures indicate that women have a somewhat lower convulsive threshold.

TYPES OF SCHIZOPHRENIA

As Strecker,[15] Kennedy[16] and Reese[17] have claimed that of the various types of schizophrenia catatonic stupor responds best to the metrazol treatment, we have tabulated our material in an attempt to correlate the diagnostic types with the therapeutic results (table 4).

In the group of treated men who improved the paranoid and the catatonic type were equally represented, with 40 per cent each. In the group of treated men who did not improve the paranoid type constituted the majority, with 62.5 per cent; the catatonic and the hebephrenic type were represented by 15 and 17.5 per cent, respectively. Of the control group of men who improved, 66.6 per cent were catatonic and 33.4 per cent hebephrenic. In the control group of men who did not improve the paranoid type led, with 45.1 per cent, followed by the catatonic type, with 29 per cent, the hebephrenic type, with 19.3 per cent, and the mixed

15. Pullar Strecker, H.: Comparisons of Insulin and Cardiazol Convulsion Therapies in Treatment of Schizophrenia, Lancet **1**:371 (Feb. 12) 1938.

16. Kennedy, A.: Convulsive Therapy in Schizophrenia, J. Ment. Sc. **83**:609 (Nov.) 1937.

17. Reese, H. H.: Hypoglycemia and Convulsive Therapy in Schizophrenia, J. A. M. A. **112**:493 (Feb. 11) 1939.

type, with 6.4 per cent. Of the group of men who improved spontaneously 83.3 per cent belonged to the paranoid type; the catatonic and the mixed type were represented by 8.3 per cent each. In the group of treated women who improved the catatonic and the paranoid type were again equally represented, with 33.3 per cent each; the hebephrenic and the mixed type were also equally represented, with 16.7 per cent each. In the group of treated women who did not improve the paranoid type was in the lead, with 43.1 per cent, followed by the catatonic type, with 34.1 per cent. The hebephrenic and the mixed type were represented by 13.6 and 9.1 per cent, respectively. There was only 1 patient in the control group of women who improved; her condition was of the mixed schizophrenic type. Of the group who did not improve 50 per cent had the paranoid, 25 per cent the catatonic, 19.4 per cent the hebephrenic and 5.6 per cent the mixed type. Of the group who improved spontaneously, 66.6 per cent had the paranoid type, and the remainder, 33.4 per cent, the hebephrenic type.

It can be stated, then, that whereas the paranoid and the catatonic type were equally represented in the treated groups, this was not the

TABLE 4.—*Relation of Types of Schizophrenia to Therapeutic Results, Expressed in Percentages*

	Men				Women			
	Paranoid	Catatonic	Hebephrenic	Mixed	Paranoid	Catatonic	Hebephrenic	Mixed
Treated, improved	40.0	40.0	20.0	....	33.3	33.3	16.7	16.7
Treated, unimproved	62.5	15.0	17.5	5.0	43.1	34.1	13.6	9.1
Control, improved	....	66.6	33.4	....	....	....	....	100.0
Control, unimproved	45.1	29.0	19.3	6.4	50.0	25.0	19.4	5.6
Spontaneously improved	83.3	8.3	....	8.3	66.6	....	33.4	....

case in the control groups. In the group who improved spontaneously the paranoid type predominated.

WEIGHT

A definite gain in weight was noted immediately after termination of a course of treatment in 80 per cent of the men who improved; in the remaining 20 per cent no change in weight took place. Of the group of treated men who did not improve only 28.2 per cent gained weight, 18 per cent lost weight and 53.8 per cent showed no change. Of the control group of men who improved, 66.6 per cent gained weight, and the weight of the other 33.3 per cent remained unchanged. Of the control group of men who did not improve, 25.7 per cent gained weight, 25.7 per cent lost weight and the remaining 49.6 per cent showed no change. Of the group of treated women who improved, 66.6 per cent gained and 33.3 per cent lost weight. Of the group who did not improve, 29.5 per cent gained and 29.5 per cent lost weight, and 40.9 per cent had no change in weight. Of the control group of women who did not improve, 30.5 per cent gained and 13.9 per cent lost weight, and the weight of 55.5 per cent remained unchanged. The 1 patient in the control group who improved gained in weight.

In summarizing, it can be said that patients who improved, both those who were treated and those who served as controls, showed a definite gain in weight, while about half the patients who did not improve showed no change in weight.

COMPLICATIONS

One patient sustained an incomplete fracture of the surgical neck of the left femur during the seventh convulsion; another, a dislocation of the left humerus during the second convulsion. Fourteen patients, 6 men and 8 women, sustained from one to seven temporomandibular dislocations during convulsions. Eight patients, 5 men and 3 women, had transitory attacks of hyperpyrexia after a convulsion, with the temperatures reaching 102 F. and lasting from two to eight hours. One patient, during the first convulsion, presented purpura covering the entire trunk and upper extremities; this disappeared forty-eight hours later. Practically every patient showed a transitory increase in systolic blood pressure immediately after cessation of a convulsion. An increase in pulse rate was also noted, lasting for the same period. A rise in systolic blood pressure and an increase in pulse rate were frequently observed immediately prior to the administration of metrazol. This was probably part of the emotional response to the injection, most of the patients displaying a frank fear reaction.

As this investigation was far advanced at the time when the compression fractures of the vertebrae following convulsions were discovered, no systematic preconvulsive and postconvulsive studies of the vertebrae were carried out.

SUMMARY AND CONCLUSIONS

A group of 100 schizophrenic patients, of whom 78 per cent had had a psychosis for more than eighteen months, underwent a course of metrazol treatment; 71 other patients, of whom 84.5 per cent had had a psychosis for more than eighteen months, were observed as controls. Fifteen more patients, of whom only 13.4 per cent had had a psychosis for more than eighteen months, improved spontaneously while in preparation for treatment. This report is based on the state of the patients from six months to one year and a half after termination of treatment or control observation.

Various degrees of improvement took place in 18 per cent of the treated patients, a much lower percentage than that generally reported.

The percentage of the various degrees of improvement in the control group was 8.4.

Relapses occurred in 11.1 per cent of the treated patients, in 33.3 per cent of the control patients and in 20 per cent of the patients showing spontaneous improvement.

The treatment was the cause of death in 1 per cent of the patients.

None of the treated or the control patients recovered. The percentage of patients with marked improvement ranged from 1.3 to 37.5 in the treated group and from 0.66 to 10 in the control group, in proportion to the duration of the psychosis. The percentage of patients who improved ranged from 5.1 to 50 in the treated group and from 3.3 to 100 in the control group, depending on the duration of the psychosis. The percentage of patients with no improvement ranged from 12.5 to 93.6 in the treated group and from 0 to 95.1 in the control group, in proportion to the duration of the psychosis.

The patients who improved spontaneously showed the best results, as measured not only by the frequency but also by the degree of improvement and by the duration of remissions.

This was the only group in which recoveries occurred, in 14.3 per cent.

Patients with a shorter duration of the psychosis had longer remissions.

The treated as well as the control patients who improved were younger than the patients who did not improve.

Women patients had a somewhat lower convulsive threshold.

In the treated group of patients who improved the paranoid and the catatonic type were equally represented; in the control group who improved the catatonic type predominated. In the treated and control groups of patients who did not improve the paranoid type predominated. In the group who improved spontaneously the paranoid type constituted the majority.

Both the treated and the control patients who improved gained in weight; about 50 per cent of the patients who did not improve showed no change in weight.

The most frequent complications observed were temporomandibular dislocations during convulsions. In 1 instance incomplete fracture of the femur and in another a dislocation of the humerus occurred. A transitory rise of blood pressure and an increase in pulse rate following a convulsion were noted in all cases.

SPASTIC PSEUDOSCLEROSIS (DISSEMINATED ENCEPHALOMYELOPATHY; CORTICOPALLIDOSPINAL DEGENERATION)

FAMILIAL AND NONFAMILIAL INCIDENCE (A CLINICOPATHOLOGIC STUDY)

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NEW YORK

Spastic pseudosclerosis was first recognized as a clinical entity by Creutzfeld [1] and Jakob.[2] Characteristic symptoms are those of pyramidal and extrapyramidal involvement, muscular atrophies and a slowly evolving mental state, usually regarded at the outset as belonging to the neuroses. Anxiety, irritability and depression are early symptoms, followed by definite changes in personality. Mild sensory disturbances have been described.

Three cases reported here are of unusual interest because of the familial incidence. This group, consisting of the cases of 2 brothers and a sister—1 of whom was previously described by one of us (Davison)—presented in life the clinical picture of spastic pseudosclerosis. The diagnosis was confirmed histopathologically in 2 of the cases. The fourth case in this presentation was of interest because of the sensory disturbances.

REPORT OF CASES

FAMILIAL TYPE.—CASE 1.—The case of J. R., a man aged 32, a brother of S. R., was previously reported clinically and pathologically by one of us (Davison).[3]

Read at a joint meeting of the New York Academy of Medicine, Section of Neurology and Psychiatry, and the New York Neurological Society, Nov. 14, 1939.

From the Neuropathological Laboratory and the Neurological Division of the Montefiore Hospital, and the Jewish Sanatorium and Hospital for Chronic Diseases.

1. Creutzfeld, H. G.: Ueber eine eigenartige herdformige Erkrankung des Zentralnervensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. **57**:1, 1920.

2. Jakob, A.: Ueber eigenartige Erkrankungen des Zentralnervensystems mit bemerkenswerten anatomischen Befunde. (Spastische Pseudosklerose-Encephalomyelopathie mit disseminierte Degenerationsherden), Ztschr. f. d. ges. Neurol. u. Psychiat. **64**:147, 1921; Spastische Pseudosklerose, in Die extrapyramidalen Erkrankungen, Berlin, Julius Springer, 1923, p. 215.

3. Davison, C.: Spastic Pseudosclerosis (Cortico-Pallido-Spinal Degeneration), Brain **55**:247, 1932.

For a detailed clinical and pathologic description of this case the reader is referred to the original article.

CASE 2.—S. R., a brother of J. R., aged 33, a musician, was first seen on Nov. 18, 1935. In March 1935 he noticed that his right leg tired easily. Three months later he began to drag the right lower extremity, and the foot would often assume an equinovarus posture; he also complained of occasional attacks of dizziness. Examination at this time revealed: flattening of the right nasolabial fold; spasticity of the right leg with scraping of the foot in walking; intention tremor in finger to nose tests; fibrillations in the right thigh and calf muscles; hyperactive tendon reflexes, more so on the right; a Hoffmann sign on the left, Rossolimo and Mendel-Bechterew signs on the right and a doubtful Babinski sign bilaterally, and the presence of the abdominal reflexes. Examination of the sensory system and cranial nerves revealed nothing abnormal.

Course.—The patient continued to work as a musician. In 1936 increased muscular rigidity of all four extremities appeared; it was less evident in the upper extremities. In June 1937 he had a severe generalized convulsion during the night. The following morning he worked as usual, but felt weak. Examination then disclosed the same findings as already recorded, with a definite Babinski sign and ankle clonus bilaterally. Thereafter, convulsive seizures, with loss of consciousness, occurred from time to time. After such attacks there was hypertonia of the right hand, with awkwardness in its use and tremulous handwriting. In the latter part of 1938 there developed marked weakness in all the muscles of the extremities and trunk, more on the right, with extreme spasticity, atrophy and fibrillations. While prior to his illness the patient had been active and interested in many social functions, he now was usually apathetic, though confident of ultimate recovery. He seemed to have a poor grasp of the situation, was self effacing, garrulous, anxious, depressed and infantile in his responses to various situations. Like the sister (case 3), he made demands on his family inconsistent with his previous solicitous attitude toward them.

Laboratory Data.—Encephalographic examination disclosed dilatation of the third ventricle, to approximately from two and a half to three times its normal width, and collections of air in the subarachnoid spaces. The Wassermann test of the blood and spinal fluid and other tests gave negative results. The total cholesterol content was 238 mg. of the blood per hundred cubic centimeters. The red and white blood cell counts were normal.

CASE 3.—D. R., a sister, was 39 years of age when she first experienced stiffness of the right leg. There then developed vertigo, difficulty in walking and dragging of the right lower extremity. Examination in December 1935 revealed fixed facies, with weakness of the right side of the face of central type, a tendency for the right foot to assume an equinovarous posture; ataxia in the finger to nose and heel to knee tests; hyperactive tendon reflexes throughout, with right ankle clonus, bilateral Oppenheim and Rossolimo signs, but no Babinski sign, and absence of abdominal reflexes. There were no disturbances of the sensory or cranial nerves. The patient was emotional, irritable and apprehensive; at times she was apathetic and showed no interest in her surroundings. She made demands on her family at great variance with the consideration she had always shown them prior to her illness.

Laboratory Data.—Serologic tests of the blood and spinal fluid; the icteric index, and the van den Bergh, galactose tolerance, blood chemistry and bromsulfthalein tests were normal.

Course.—When the patient was seen again in March 1937, examination disclosed: marked rigidity and spasticity; atrophy and fibrillations in the muscles of the extremities; exaggeration of the tendon reflexes, with a Babinski sign bilaterally; fixed facies, and monotonous speech. The mental picture became accentuated, but at no time did the patient show signs of dementia. She died on June 16, 1937.

Macroscopic Examination.—Brain: The brain weighed 975 Gm. There were slight atrophy of the frontal and marked atrophy of the motor and parietal

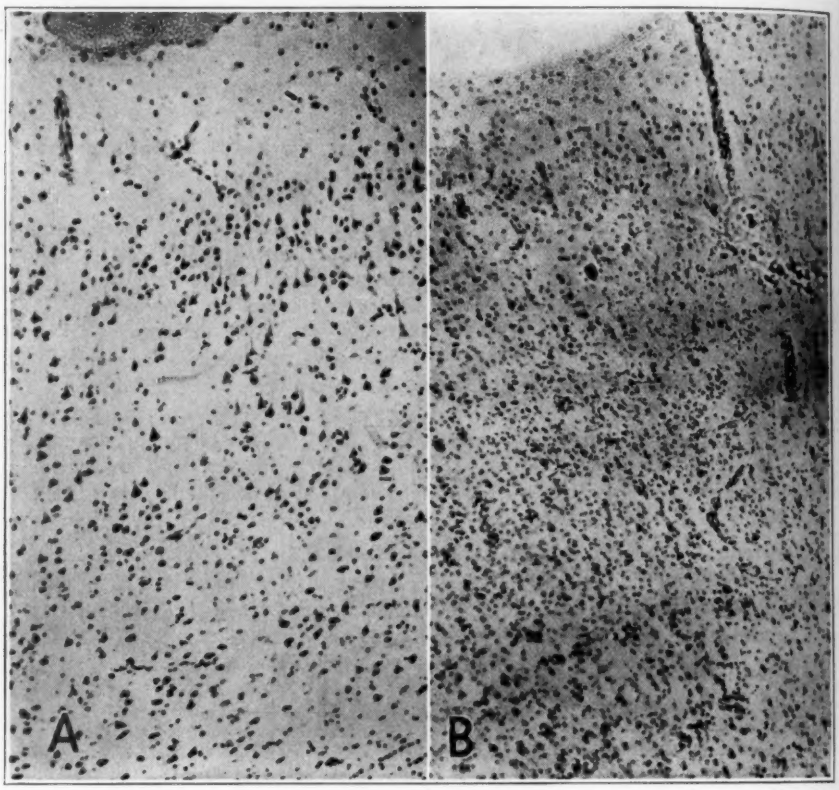

Fig. 1.—Distortion in the cytoarchitectural arrangement of the cortical layers. *A*, frontal cortex, showing dropping out of nerve cells; × 45. *B*, motor cortex, showing increase in microglia; × 36. Cresyl violet stain.

convolutions, especially on the left side; the occipital convolutions appeared normal. The vessels at the base were normal. The brain was cut coronally. There was slight uniform dilatation of the entire ventricular system; the left lateral ventricle, including the posterior horn, was slightly more dilated than the right. In sections through the parieto-occipital region the left posterior horn was about four times the size of the right. The caudate nucleus and putamen were slightly shrunken. The substantia nigra appeared normal.

Microscopic Examination.—Sections from various cortical regions, the diencephalon, the mesencephalon, the metencephalon and the cervical region of the cord were embedded in pyroxylin and stained by myelin sheath and cresyl violet methods. Frozen sections were also stained by the Spielmeyer, Bielschowsky, Holzer and sudan III methods.

Cerebral Cortex: Frontal convolutions: The meninges were normal. There was slight distortion in the arrangement of the cytoarchitectural layers. A few areas of devastation, diminution in the number and complete disappearance of nerve cells (fig. 1 *A*) were the outstanding features. Some of the nerve cells were shrunken; others showed chromatolytic changes. This process was most marked in the third cortical layer.

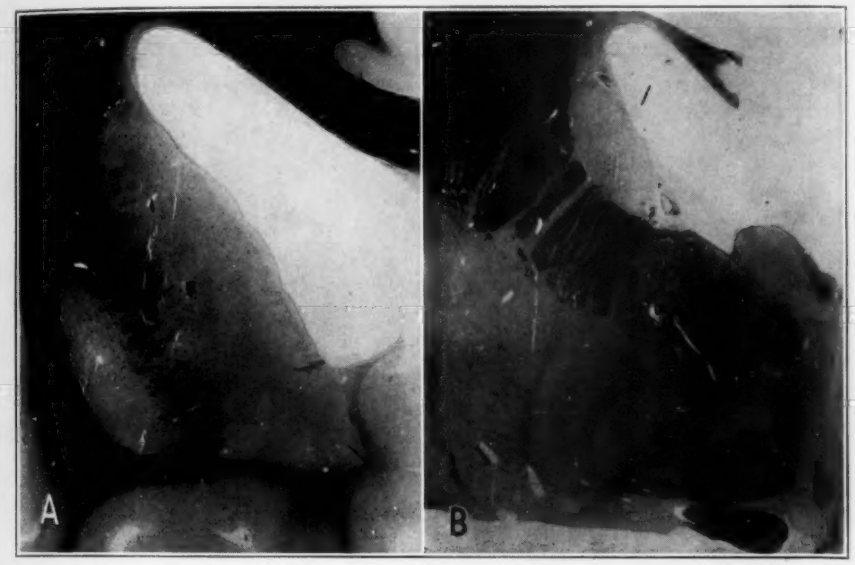

Fig. 2.—*A*, shrinkage of the caudate nucleus and the putamen, especially the latter, and dilatation of the lateral ventricle. *B*, demyelination, especially of the outer segment of the globus pallidus, shrinkage of the caudate nucleus and thinning of the ansa lenticularis. Notice the intactness of the internal capsule. Myelin sheath stain.

Premotor Region: In sections through the premotor region, in addition to the preceding changes, there was also an increase in the microglia cells. Some of the large pyramidal cells contained hardly any Nissl substance; others showed complete disintegration (fig. 3 *A*).

Motor Region: The meninges in places were distended and slightly thickened, owing to proliferation of the arachnoid cells. There were marked distortion in the arrangement of the cytoarchitectural layers, increase in the microglia cells (fig. 1 *B*), disappearance of nerve cells and all types of pathologic changes, such as chromatolysis, shrinkage, pyknosis and satellitosis. The microglia cells in many regions were rod shaped. A few of the vessels of the white matter were calcified.

Parietal, temporal and hippocampal convolutions: Sections from these areas showed approximately the same changes. Numerous amyloid bodies were observed near the temporal horns. The occipital convolutions showed no outstanding changes.

Diencephalon: In various coronal sections through the diencephalon there were shrinkage of the putamen and caudate mucleus (fig. 2 *A*), pallor of the pallidal segments (fig. 2 *B*) and thinning of the ansa lenticularis (fig. 2 *B*). With a higher

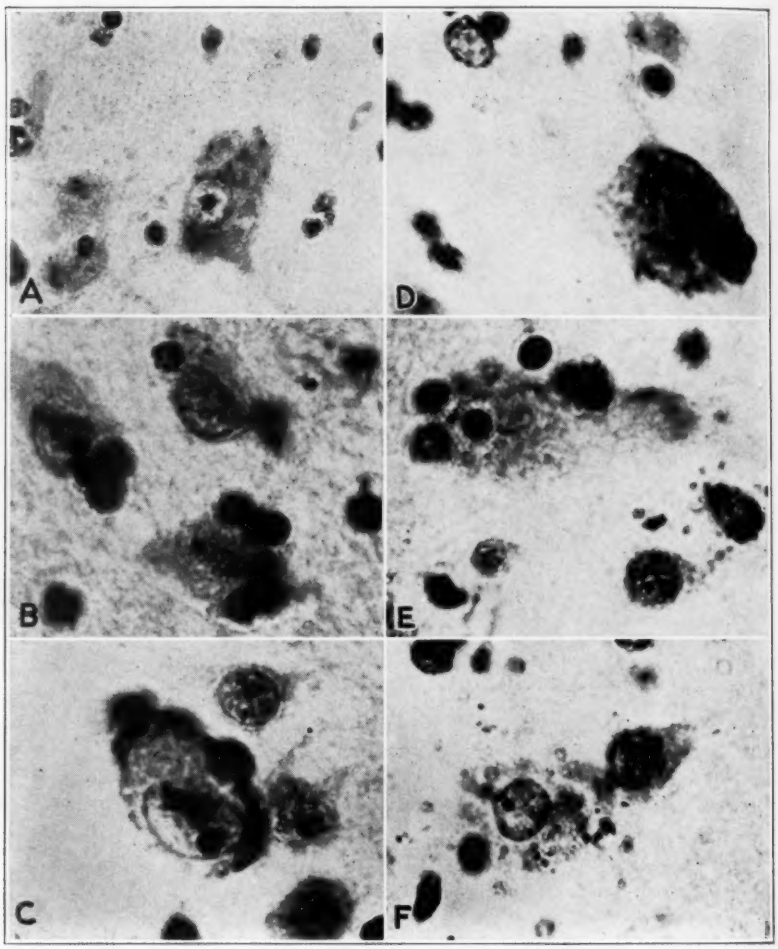

Fig. 3.—*A*, two diseased pyramidal cells of the premotor convolution, one of which is almost completely disintegrated; × 400. *B*, nerve cells of the striatum, showing neuronophagia and satellitosis, one appearing as a shadow cell; × 700. *C*, nerve cell of the striatum showing chromatolysis, disintegration and collections of Nissl substance at the periphery; × 700. *D*, nerve cell of the striatum undergoing disintegration and one Alzheimer glia cell, type II; × 700. *E*, disintegrated nerve cell of the pallidum, appearing as a shadow cell; × 700. *F*, typical Alzheimer glia cells surrounded by pigment granules; × 700. Cresyl violet stain.

power some of the myelin fibers within the pallidal segments appeared disintegrated. In cresyl violet preparations the nerve cells of the striatum were decreased in number and showed disintegration, neuronophagia, chromatolysis and peripherally displaced nuclei (fig. 3 *B*, *C* and *D*); this process was more severe in the large ganglion cells. There was an increase in the microglia cells. Pigmentary deposits were observed around some of the large and small ganglion cells. An occasional Alzheimer glia cell of type I or II was also observed (fig 3 *F*). In sections through the same regions, in sudan III preparations, fatty deposits in and widening of the perivascular spaces (fig. 4) were observed in the following regions: the external capsule, gyrus cinguli, centrum ovale and internal capsule. With this

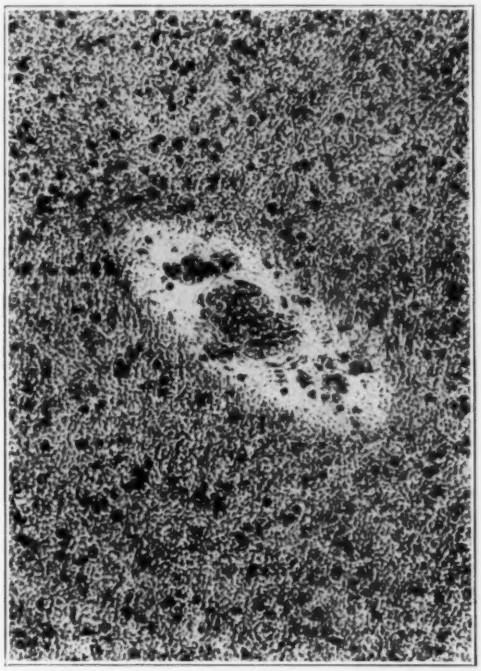

Fig. 4.—Fatty deposits in and widening of the perivascular spaces. Sudan III; × 150.

stain the nerve cells of the striatum and pallidum did not appear to contain any lipoid deposits. Holzer preparations disclosed slight gliosis in the caudate nucleus. In Bielschowsky preparations some of the axis-cylinders in the pallidum and internal capsule were slightly disintegrated.

The pallidal nerve cells were pale and appeared as shadow cells (fig. 5 *A*). Some showed satellitosis, neuronophagia or complete destruction, while others were surrounded by heavy deposits of pigment granules and Alzheimer glia cells (figs. 3 *E* and 5 *B*). The hypothalamic nerve cells appeared normal except for slight poverty in pigment granules. The nerve cells of the thalamic nuclei showed no abnormality.

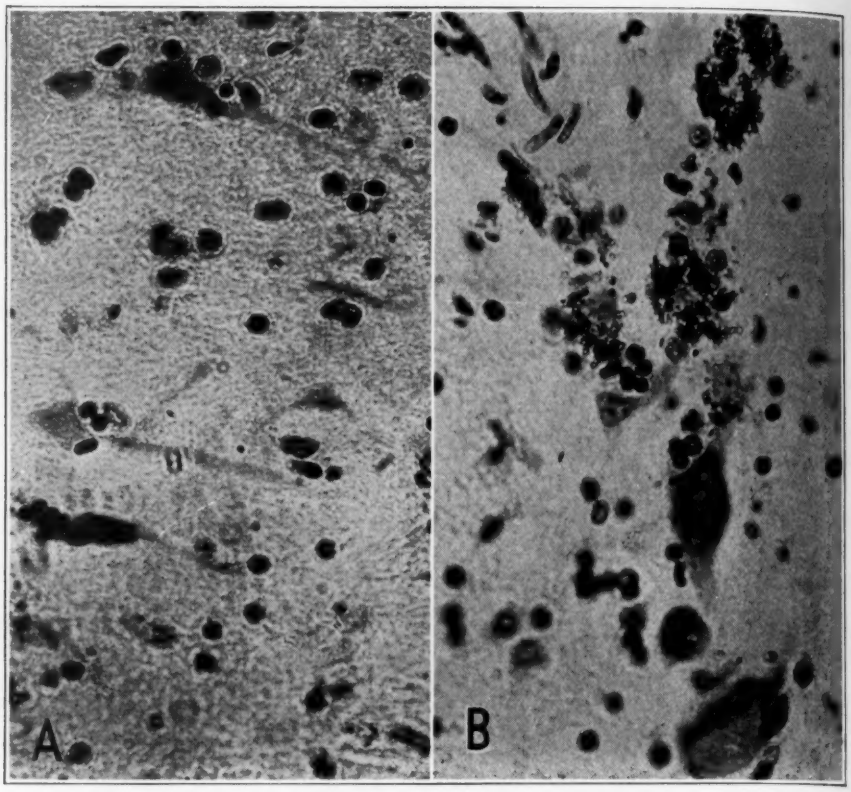

Fig. 5.—*A*, pallidal nerve cells showing satellitosis and beginning neuronophagia. Some appear as shadow cells. × 216. *B*, pigment accumulations. Alzheimer glia cells and diseased nerve cells of the pallidum. Some are completely obliterated by pigment granules. × 432. Cresyl violet stain.

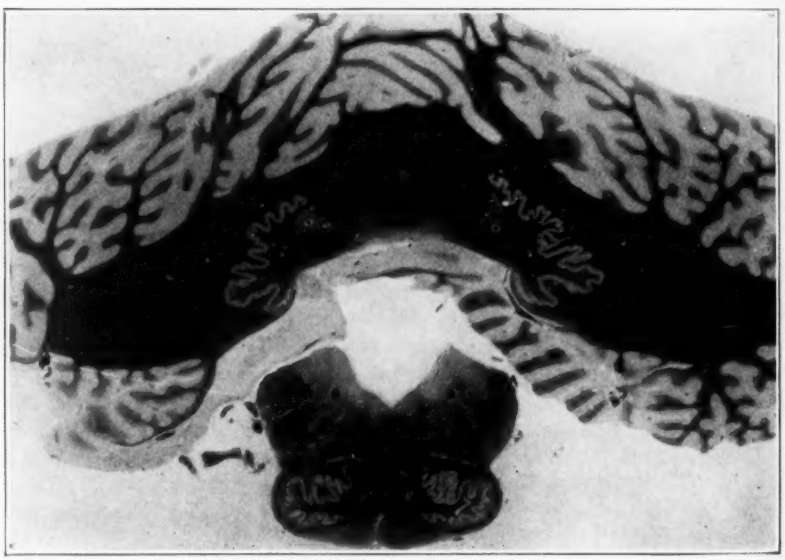

Fig. 6.—Section of the medulla oblongata through the fourth ventricle, showing bilateral demyelination of the pyramids. Myelin sheath stain.

Red Nucleus and Substantia Nigra: No changes were noted in myelin sheath preparations. In cresyl violet preparations the nerve cells of the red nucleus were smaller than usual and were somewhat deficient in Nissl substance. The nerve cells of the substantia nigra were normal, but some did not contain the normal amount of iron pigment. The nerve cells of the corpus Luysi stained poorly.

Mesencephalon and Metencephalon: There was slight degeneration of the pyramidal fibers. The nerve cells of the locus caeruleus did not contain the heavy deposits of pigment usually seen. In lower sections of the pons both pyramids were demyelinated.

Cerebellum, Dentate Nucleus and Medulla Oblongata: There was demyelination of both pyramids in the medulla oblongata, with all types of destruction of myelin (fig. 6) and a slight honeycombed appearance. The nerve cells of the various nuclei of the cranial nerves and of the inferior olivary nuclei were normal. The ganglion cells of the dentate nucleus disclosed an occasional pallor and pigment atrophy. The cerebellum was normal. In sections through the crossing of the pyramids, there was bilateral degeneration of the pyramids (fig. 7 *A*), on the right more than on the left.

Spinal Cord.—Only the upper cervical part of the cord was obtained at autopsy. There was demyelination of the crossed and anterior pyramidal tracts, more on the right than on the left (fig. 7 *B*). The myelin in these pathways showed all types of destruction. The anterior horn cells were normal except for occasional pyknosis or chromatolysis. In sudan III preparations the demyelinated pathways were filled with compound granular corpuscles, some surrounding the perivascular spaces. There was no evidence of any inflammatory cells. In Holzer preparations the demyelinated pathways showed slight gliosis.

Nonfamilial Type.—Case 4.—B. S., a married woman aged 53, who had been born in Poland, was admitted to the Montefiore Hospital on Sept. 14, 1935. In May 1932 she had experienced difficulty, slowness and heaviness in gait and marked diminution in power of the lower extremities. In 1934 she complained of numbness and tingling in the interscapular region. A few months later power of the upper extremities became markedly impaired. Since July 1935 she had complained of stiffness of the neck. There was no history of mental or nervous disorder in the family. A diagnosis of "kidney stone" was considered in 1928, on the basis of pain in the loin, burning and frequency and urgency of micturition associated with hematuria. The patient improved within two months. In 1930 these symptoms recurred; occasionally they were accompanied by chills, fever and dysuria. At this time pus was found in the urine.

General Physical Examination.—No abnormality was found. The systolic blood pressure was 100 and the diastolic 60.

Neurologic Examination.—At the time of admission the patient was alert, pleasant, intelligent and cooperative; there was no evidence of any mental symptoms. There was some loss in motor power with spasticity of the upper and lower extremities, but there were no atrophies or fibrillations. All tendon reflexes were hyperactive, and there were positive Babinski and allied signs and absence of abdominal reflexes. Spontaneous pains were present in the neck. Sensory examination disclosed: pallanesthesia in the left leg and thigh, pallhypesthesia in the right leg, a band of slight hyperesthesia and hyperalgesia from the fourth to the seventh cervical segment, generalized diminution of all forms of sensation from the trunk down and absence of vibratory sensation in the toes of the left foot and diminution up to the knees. There was incontinence of urine. The pupils were equal and

reacted to all stimuli. The cranial nerves were normal. During this examination diagnoses of neoplasm in the high cervical portion of the cord, and vascular or degenerative diseases of the spinal cord were considered.

Laboratory Data.—The red and white blood cell counts were normal, and the Wassermann reactions of the blood and spinal fluid were negative. Examination

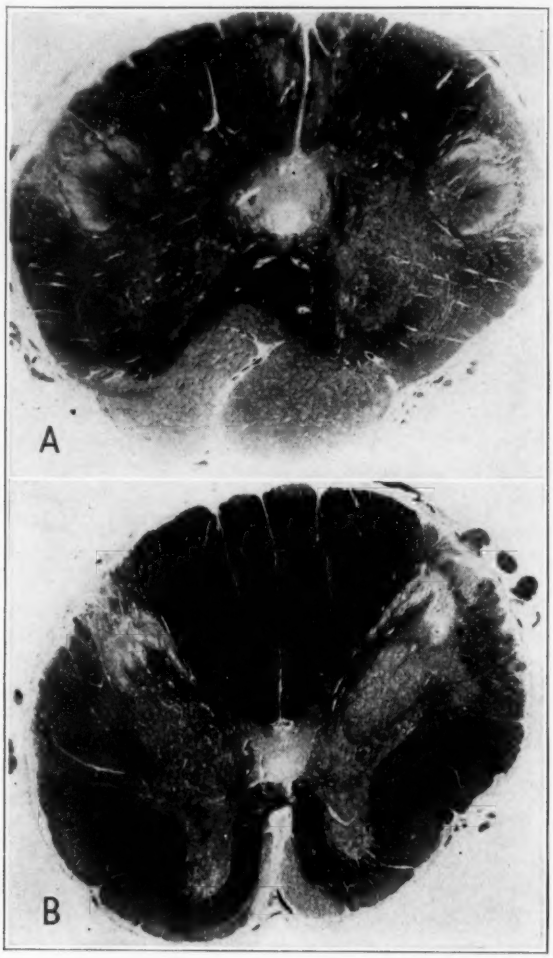

Fig. 7.—*A,* section of the medulla oblongata through the crossing of the pyramids, showing bilateral demyelination of the pyramids. *B,* section of the cervical portion of the cord slightly below the decussation of the pyramids, showing demyelination of the lateral and anterior pyramidal tracts. Myelin sheath stain.

of the spinal fluid showed: 38.2 mg. of protein per hundred cubic centimeters; a negative gum mastic curve; an Ayala index of 3.6; an initial pressure of 100 mm., and a final pressure of 30 mm. Roentgen examination revealed slight hypertrophic spondylitis of the cervical portion of the spine.

Course.—Findings in the sensory examinations always varied and were seldom definite. On Oct. 20, 1935, fibrillations were first noted in the ulnar aspect of the right hand. The extremities became markedly spastic, the right and left upper extremities more than the lower. On Nov. 5, 1935, the patient showed a typical parkinsonian picture: masklike facies, rounding of the shoulders and almost absolute fixation of the entire body. In addition, there were: turning en masse on movement; abduction of the arms at the shoulder with elbow flexion and pronation and partial flexion of the fingers; loss of associated movement bilaterally; cogwheel rigidity, more marked on the right; tremor of the fingers, but no ataxia, and bilateral pronator signs. At this time there was noted atrophy of the muscles of the hypothenar eminences. The signs of involvement of the pyramidal tracts remained unchanged. On Dec. 10, 1936, slight "pill-rolling" movements appeared. The atrophy extended to the muscles in the suprascapular and infrascapular regions and thenar eminences and the interosseus muscles. Sensory examination revealed no change. On June 5, 1937, the extrapyramidal symptoms became more advanced, and the patient became apathetic, negativistic and somewhat drowsy, a state from which she could easily be aroused. She refused to answer questions of physicians and nurses, expressed no complaints and showed some loss in memory, which was best brought out in her conversations with visitors. She died on July 12, 1937.

Macroscopic Examination.—Brain: Except for atrophy of all frontal convolutions, there were no visible abnormalities. The brain was cut coronally. There were slight dilatation of the lateral ventricles and translucence and yellowish discoloration of the medulla oblongata.

Spinal Cord: Segments of the spinal cord only from the lower dorsal and the lumbosacral region were obtained. The pyramidal tracts appeared transulcent.

Microscopic Examination.—Complete coronal sections through the frontal convolutions, sections from various cortical regions, the diencephalon, the mesencephalon, the metencephalon and the spinal cord were embedded in pyroxylin, cut and stained by the myelin sheath and cresyl violet methods. Some of these sections were frozen and stained by the Spielmeyer, Bielschowsky, sudan III and Holzer methods.

Cerebral Cortex: Frontal convolutions: No abnormality was noted in myelin sheath preparations. In cresyl violet sections there were areas of devastation, congestion of the blood vessels, slight distortion in the arrangement of the cytoarchitectural layers and dropping out of many of the nerve cells, most noticeable in the second and third cortical layers. The remaining ganglion cells stained poorly. Occasional satellitosis and neuronophagia were also noted. In some regions there was a slight increase in microglia cells. The meninges throughout were normal, except for occasional edema and proliferation of the arachnoid cells. The walls of the vessels were normal.

Motor, Temporal, Hippocampal and Occipital Convolutions: Sections from these areas showed only slight edema of the white matter, but the nerve fibers appeared preserved. The arrangement of the cytoarchitectural layers was normal, and the giant pyramidal cells of Betz in the motor region were intact.

Parietal Convolutions: Sections through the parietal region disclosed marked pallor of the white matter (fig. 8 *A*). With high magnification the myelin fibers were observed to have stained poorly and to be slightly disintegrated, especially in the vicinity of the perivascular spaces. A similar process was noted in the region of the paracentral lobule. In places the white matter had a slightly honeycombed appearance. In cresyl violet preparations the cytoarchitectural arrangement of the parietal cortex appeared slightly distorted. There were dropping out

of ganglion cells and a slight increase of the microglia cells. Occasional proliferation of the small cortical vessels was noted. Some of the perivascular spaces in the white matter were widened and contained a slight accumulation of pigment granules. The oligodendroglia cells were slightly swollen.

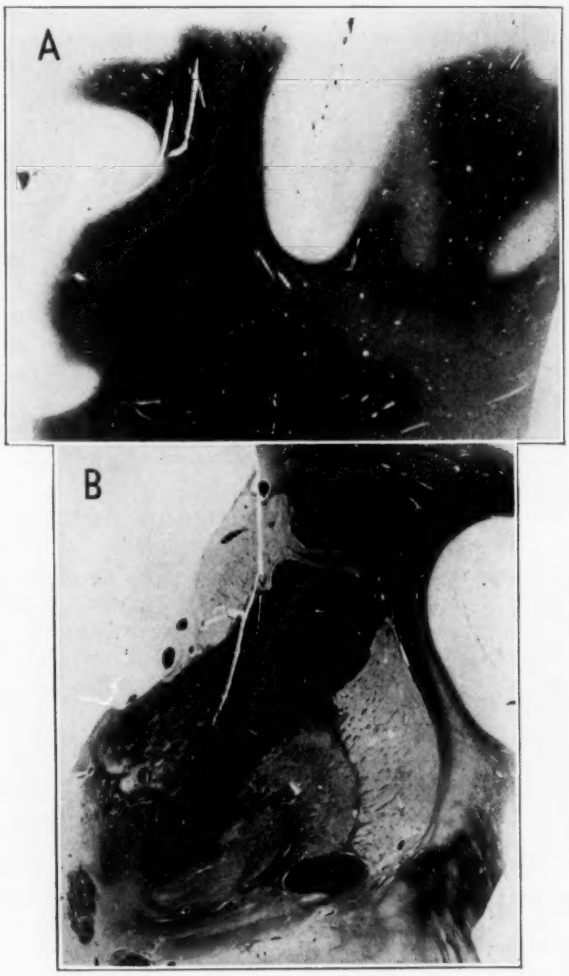

Fig. 8.—*A*, small area of demyelination in the white matter of the parietal convolutions. *B*, slight demyelination of the pallidal segments and lacunar appearance of the pallidum and of the putamen. Myelin sheath stain.

Diencephalon: In myelin sheath preparations of sections passing through the striatum and pallidum there were slight thinning of the ansa lenticularis, pallor of the pallidal segments, especially the outer (fig. 8 *B*), a lacunar appearance of the putamen and the outer segment of the pallidum and widening of the perivascular spaces of the putamen and the pallidum (fig. 9 *A*). In cresyl violet prepara-

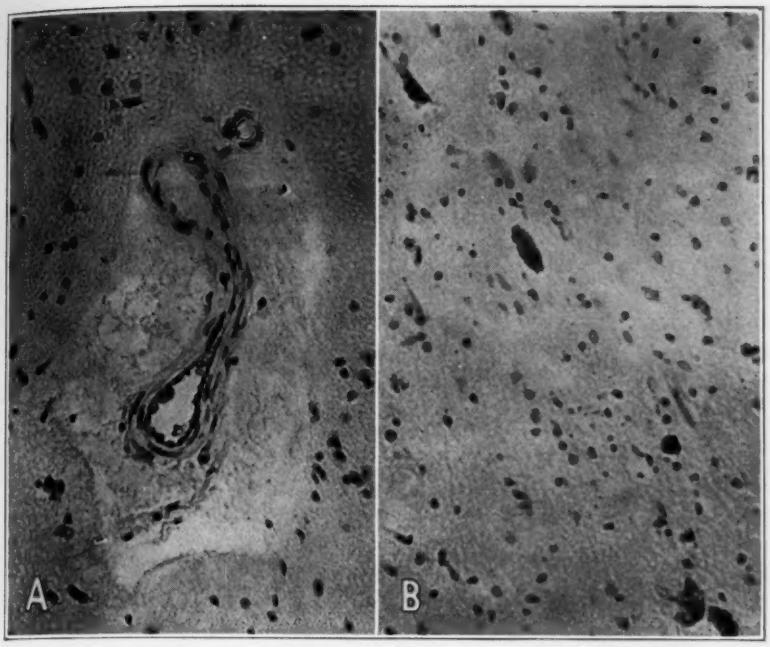

Fig. 9.—*A*, widening of the perivascular spaces. *B*, diminution in the number of nerve cells of and loss of pigment granules in the substantia nigra. Cresyl violet stain; × 170.

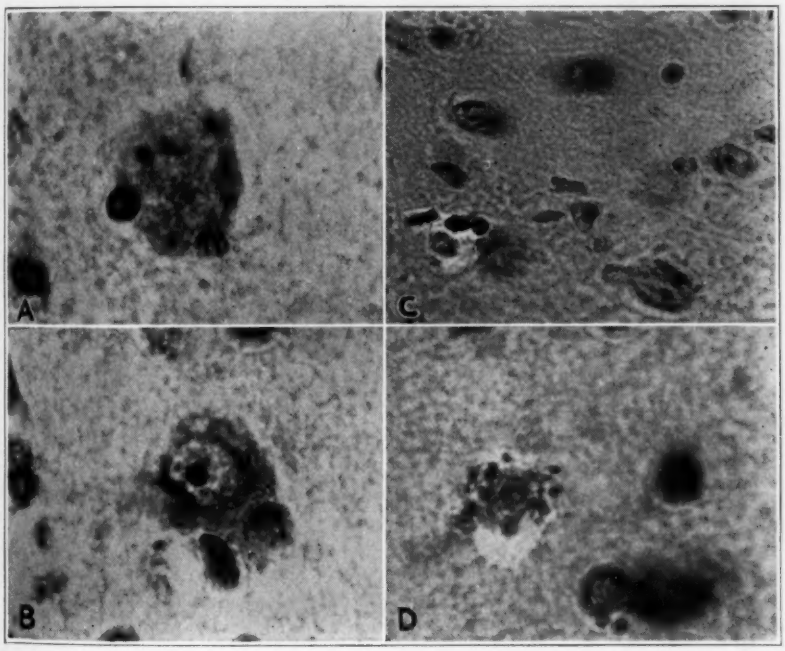

Fig. 10.—*A* and *B*, nerve cells of the striatum undergoing chromatolysis; × 765. *C*, nerve cells of the pallidum appearing as shadow cells, some of which are completely disintegrated; × 380. *D*, Alzheimer glia cell with pigment accumulation; × 765. Cresyl violet stain.

tions there were slight edema, partial destruction and disintegration of the large cells of the putamen and caudate nucleus (fig. 10 *A* and *B*) and occasional Alzheimer glia cells, types I and II (fig. 10 *D*). The disintegrated large nerve cells also had the appearance of Alzheimer glia cells. Chromatolysis (fig. 10 *A*), neuronophagia and satellitosis were also noted. The smaller ganglion cells were better preserved. Many of the pallidal nerve cells had either disappeared or stained poorly (fig. 10 *C*); some appeared merely as shadow cells (fig. 10 *C*),

Fig. 11.—Section of the medulla oblongata through the fourth ventricle, showing bilateral demyelination of the pyramids.

and others were completely disintegrated; a few of the cells stained well. Alzheimer glia cells, as noted in the putamen, were also seen in the pallidum (fig. 10 *D*). Some of the vessels showed pigmentary deposits. Occasional proliferation of the vessels of the pallidum and the putamen was also observed. In some sections there was a marked increase in the glia nuclei. There was calcification of the walls of some of the pallidal blood vessels. Numerous agonal hemorrhages were present in the thalamus and hypothalamus; the thalamic and hypothalamic nerve cells, however, were normal. In sudan III preparations occasional fatty deposits

were observed in the perivascular spaces of the striatum and pallidum. In Holzer preparations there was slight perivascular gliosis in these structures.

Substantia Nigra and Red Nucleus: No abnormality was noted in myelin sheath preparations of sections passing through these regions. In cresyl violet preparations, there were diminution, destruction and poverty in the pigment granules of the nerve cells of the substantia nigra (fig. 9 *B*). In places there was an increase in the glia nuclei. There was also widening of the perivascular spaces (fig. 9 *A*). The ganglion cells of the corpus Luysi were normal. The red nucleus was the seat of numerous agonal hemorrhages, similar to those noted in the hypothalamus. The ganglion cells of the red nucleus stained poorly and showed loss of chromatin.

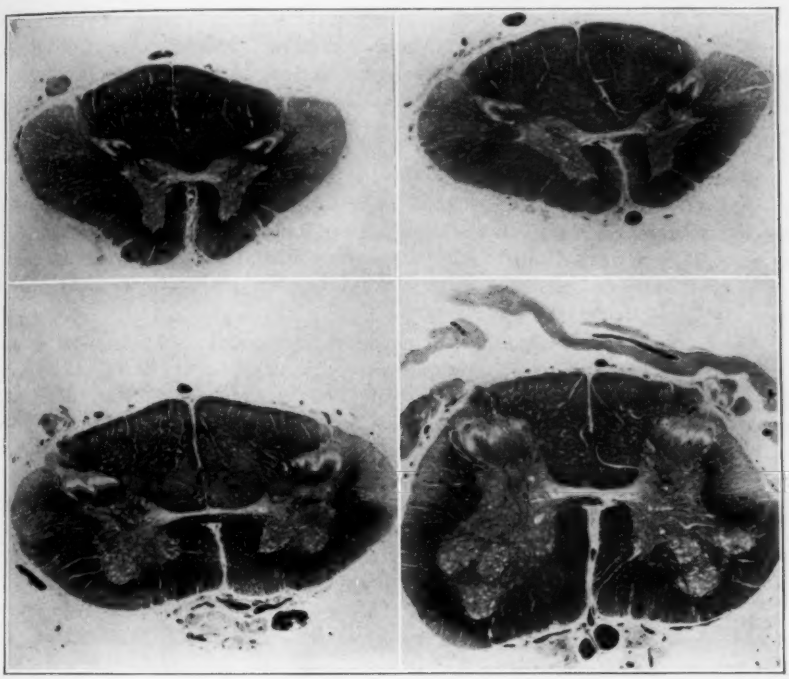

Fig. 12.—Sections of the spinal cord through the lower dorsal and the lumbosacral regions, showing bilateral degeneration of the lateral pyramidal tracts. Myelin sheath stain.

Mesencephalon: No abnormality was noted in myelin sheath preparations of sections passing through the aqueduct. In cresyl violet preparations the nerve cells of the locus caeruleus were devoid of pigment granules. Edema of the perivascular spaces and some agonal hemorrhages were present. In sections slightly below this no abnormality was noted except pallor and occasional disintegration of the pyramidal fibers and marked prominence of the arcuate nuclei. The nerve cells, however, were normal.

Cerebellum and Dentate Nuclei: There were no abnormalities in myelin sheath preparations. The Purkinje cells in the cerebellum stained poorly. There were widening of the perivascular spaces and occasional accumulation of compound granular corpuscles. The nerve cells of the dentate nucleus were normal.

Metencephalon: In sections of the medulla oblongata, at the level of the nuclei of the sixth and seventh cranial nerves, aberrant arcuate nuclei were present between the pyramids. The pyramidal fibers stained poorly, but showed only disintegration of single myelin fibers. In sections below this level the pallor of the pyramids was more marked (fig. 11); the myelin sheaths and axis-cylinders showed all types of pathologic changes. In cresyl violet preparations a slight increase of the glia nuclei was observed in some regions of the pyramids. The nerve cells of the nuclei of the medulla oblongata were intact, except those of the nucleus of the twelfth nerve, which were slightly shrunken and pyknotic. The vessels throughout the wall of the fourth ventricle were congested. In sections through the crossing of the pyramids there was pallor of the pyramids, with changes similar to those already described.

Spinal Cord: Sections from the lower dorsal and lumbosacral region of the spinal cord showed demyelination of both pyramidal tracts, more marked on the right than on the left (fig. 12). The myelin in the pyramidal tracts was disintegrated and showed all types of pathologic changes. The axis-cylinders were fragmented and swollen and had corkscrew processes. Occasional disintegration of myelin fibers was also noted in the sensory pathways. In cresyl violet preparations numerous agonal hemorrhages were observed throughout the gray matter. A few of the anterior horn cells showed pigment atrophy, disintegration and vacuolation. Agonal subarachnoid hemorrhages were present in the gray matter. In sudan III preparations the demyelinated areas in the pyramidal and sensory pathways were filled with compound granular corpuscles. In Holzer preparations slight gliosis was present in the pyramidal pathways.

Comment.—The mental, extrapyramidal (parkinsonism) and pyramidal symptoms, atrophy of the muscles and vague sensory disturbances combined with pathologic changes, demonstrable in the frontal and parietal convolutions, the basal ganglia, the substantia nigra, the pyramidal and sensory pathways and the anterior horn cells, indicate that the case is one of spastic pseudosclerosis. The atrophy of muscles was most marked in the upper extremity; unfortunately, the anterior horn cells of the corresponding segment could not be studied, as only part of the lower dorsal and lumbosacral region was obtained at autopsy. The scattered sensory disturbances observed clinically were undoubtedly the result of the degenerations observed in the few segments of the spinal cord available for study.

COMMENT

As will be seen in the cases reported here and those previously recorded in the literature, spastic pseudosclerosis occurs mostly in the fourth and fifth decades of life. A familial or hereditary incidence has not been reported in more than 2 instances. In Meggendorfer's [4] case there was a familial history of paralysis affecting 7 of 9 aunts on the mother's side. The mother of the patient, at the age of 54, also presented mental symptoms, and a brother, whose case was reported by Kirschbaum,[5] at the age of 44, suffered from the same disease as the

4. Meggendorfer, F.: Klinische und genealogische Beobachtungen bei einem Fall von spastischer Pseudosklerose Jakobs, Ztschr. f. d. ges. Neurol. u. Psychiat. **128**:337, 1930.

5. Kirschbaum, W.: Zwei eigenartige Erkrankungen des Zentralnervensystems nach Art der spastischen Pseudosklerose (Jakob), Ztschr. f. d. ges. Neurol. u. Psychiat. **92**:175, 1924.

patient. Worster-Drought [6] and his associates described a case of familial presenile dementia with spastic paralysis. The disease, in this instance apparently transmitted through the female side and spreading over three generations, was traced to 9 members of the family.

In the majority of instances the motor disturbances appear first in the form of paresis, gradually leading to spastic paralysis with signs of involvement of the pyramidal tracts. Atrophies and fibrillations of muscles, as in our cases, have been reported in a few instances. Later, or about the time of involvement of the pyramidal system, there appear extrapyramidal symptoms. These usually consist of spontaneous movements, rigidity, tremor and athetosis, and disturbances in muscle tonus alternating between hypotonia and hypertonia. In most of the recorded cases tremor has been an early and pronounced symptom. The typical parkinsonian syndrome, as in some of our cases, has also been described. Speech may become slow, montonous and dysarthritic. This was noted in about half the recorded cases. In the 2 cases previously reported by one of us (Davison [3]) such a disturbance was shown. Vague subjective and objective sensory disturbances, as observed in case 4, were also noted by Jansen and Monrad-Krohn [7] and others. The mental symptoms usually appear after the onset of the pyramidal and extrapyramidal symptoms. At first, the patients may show only slight changes in personality, such as anxiety, irritability, depression and insomnia. Toward the end the mental symptoms become more marked and consist of apathy, negativism, delirium, confusion, visual and auditory hallucinations, confabulations which remind one of Korsakoff's syndrome, and occasionally euphoria. The terminal picture is that of severe dementia. In a few cases the mental symptoms appeared before the motor disturbances; as they were slight, a diagnosis of psychoneurosis was the first consideration. A Kayser-Fleischer corneal ring was recorded in some instances; it is doubtful whether these cases belong to this group. The findings in the blood and cerebrospinal fluid were normal in practically all recorded cases. Involvement of the bulbar nuclei, decubitus, marked stupor and fever usually bring the illness to an end.

Remissions occur in many instances. The illness usually lasts from several weeks to about two years. In the cases in the familial group reported by Worster-Drought and others the longest period of survival was thirteen years, the shortest two years and the average eight years. The longest period of survival in most of the other cases was about four years. It is possible that many of the cases in the familial group

6. Worster-Drought, C.; Hill, T. R., and McMenemey, W. H.: Familial Presenile Dementia with Spastic Paralysis, J. Neurol. & Psychopath. **14**:27, 1933.

7. Jansen, J., and Monrad-Krohn, G. H.: Ueber die Creutzfeld-Jakobsche Krankheit, Ztschr. f. d. ges. Neurol. u. Psychiat. **163**: 670, 1938.

described by Worster-Drought and his associates were those of some other disease of the central nervous system.

Pathologically, there are widespread lesions through the central nervous system, including mainly the frontal and precentral convolutions, the striatum and pallidum, and at times the thalamic nuclei, the pyramidal system, the bulbar nuclei and the anterior horn cells. The sensory system, as in case 4 in our series, may also be involved. The histopathologic picture consists of distortion in the arrangement of the cytoarchitectural layers of the affected convolutions, areas of devastation, noncharacteristic changes in the ganglion cells, slight proliferation of the glial elements and destruction of the myelin sheaths and axis-cylinders in the pyramidal and extrapyramidal pathways. Since the changes in the pyramidal tracts are present throughout their course, these alterations are probably the result of disease of the giant pyramidal cells of Betz. In case 1, that of the brother of the patient in case 3, previously described by one of us (Davison), the degeneration of the pyramidal pathways was observed only in the pyramids of the medulla oblongata and the corticospinal tracts of the cord. In a few instances, as in case 3 of the present series, pigmentary deposits around the ganglion and glia cells and perivascular spaces and Alzheimer glia cells of types I and II have also been reported. Inflammatory reactions and specific changes in the blood vessels have not been observed in our cases, but in some of the cases described by others a reactive inflammatory process appeared in places.

The disease must frequently be differentiated from the presenile psychoses (Alzheimer's and Pick's disease), dementia paralytica, amyotrophic lateral sclerosis, progressive hepatolenticular degenerations (Wilson's disease and Westphal-Strümpell pseudosclerosis), dementia praecox and multiple sclerosis.

In the presenile psychoses (Alzheimer's and Pick's disease) the mental symptoms are more marked, while the symptoms of disturbance in the extrapyramidal and pyramidal tracts are rare accompaniments. Lower motor neuron disease, as far as we know, has never been described in cases of these disorders. Histopathologically, the picture in the presenile psychosis is different from that seen in spastic pseudosclerosis and should not lead to confusion.

Amyotrophic lateral sclerosis in its terminal state, sometimes associated with mental symptoms, may be confused with this syndrome. The absence of extrapyramidal symptoms should be of help in differentiation of the two diseases. The cases of amyotrophic lateral sclerosis following chronic encephalitis, described by Wimmer and others, when mental symptoms are presented may afford difficulty in differentiation from cases of spastic pseudosclerosis, but a history of encephalitis may be elicited in the former.

The disease is difficult to differentiate from the progressive hepatolenticular group (Wilson's disease and Westphal-Strümpell pseudosclerosis). Mental symptoms, and occasionally even pyramidal tract signs, may appear in the hepatolenticular degenerations; disease of the anterior horn cells, however, is absent. To our knowledge, the Kayser-Fleischer corneal ring observed in Westphal-Strümpell pseudosclerosis is not seen in spastic pseudosclerosis. In none of our 5 cases was there pigmentation at the corneoscleral junction. The liver was normal in 3 of the 4 cases we have studied histopathologically; in 1 it was not obtained at autopsy. A few of the cases of pseudosclerosis reported in the literature (von Economo and Schilder, and Woerkom) with changes in the liver were diagnosed by some as cases of spastic pseudosclerosis. It is probable that these were true instances of hepatolenticular degeneration. Histopathologically, except for the hepatic changes, the differentiation may be difficult, as Alzheimer glia cells and other changes in the striopallidal structure may be seen in spastic pseudosclerosis.

The differentiation from dementia paralytica, dementia praecox and multiple sclerosis is less difficult. In 2 of our cases the disease was considered at one time as multiple sclerosis, but this diagnosis was ruled out as the disease progressed.

As can be seen, the original term spastic pseudosclerosis is not descriptive for this syndrome, either from the clinical or from the pathologic point of view. The process consists of disseminated encephalomyelopathy involving the cortex, the extrapyramidal and pyramidal systems and the anterior horn cells. As there are many other disorders of disseminated encephalomyelopathy which present a different clinical picture, this syndrome could be designated as disseminated encephalomyelopathy, spastic pseudosclerosis or corticopallidospinal degeneration.

CONCLUSION

Four cases of spastic pseudosclerosis are reported, in 3 of which the disease occurred in members of the same family. Clinically, disease of the pyramidal and extrapyramidal systems and the anterior horn cells and mental symptoms were present in all. In 1 instance there were also sensory disturbances. The mental symptoms in all of these cases appeared last. Hispathologically, changes were observed in the frontal, premotor, motor and parietal convolutions, in the pyramidal and extrapyramidal systems and in the lower motor neurons.

DISCUSSION

DR. MOSES KESCHNER, New York: If there is such a clinicopathologic entity as spastic pseudosclerosis, Dr. Davison and Dr. Rabiner have made a valuable contribution to knowledge of its clinical and pathologic features. Judging from their cases, the disease apparently may begin much earlier than the fourth decade

of life, as was originally stated by Creutzfeld and Jakob, who first described the disorder. This is also borne out by the literature. Cases have been reported in which the disease made its first appearance at the age of 10 years and the clinical as well as the pathologic findings were, with minor exceptions, practically the same as in the present cases.

The familial incidence in the cases reported here may be of significance in the pathogenesis of the condition. Schaeffer was the first to include it among the heredogenerative diseases. He saw in the disorder a peculiar predilection of the pathologic process for certain ectodermal structures. Jakob, in discussing the nosologic characteristics of the disease, also emphasized that it attacked only motor systems. In this sense, he suggested that it might be a heredogenerative disease, although he stated that he did not care to commit himself with respect to this phase of the problem. In the future, genetic studies combined with clinicopathologic considerations may shed light on the pathogenesis of the condition.

Various agents have been considered as causative factors in the disease. Nutritional disturbances of the nervous system in the nature of deficiency diseases and toxins, both endogenous and exogenous, have been regarded as possible etiologic factors; thus far, however, no satisfactory evidence has been adduced in favor of this theory. Jakob for a while considered the condition as a possible variant of epidemic metencephalitis and, in his monograph on extrapyramidal diseases, stated that until such time as one knows definitely the etiologic agent in epidemic encephalitis this question cannot be answered with any reasonable certainty. Some authors have expressed the belief that the disease represents premature senescence of the nervous system; on histologic grounds, however, it would seem that this is not the case.

Dr. Davison and Dr. Rabiner have given a good résumé of the clinical features of the disease. In view of the multiplicity of the lesions, the symptoms may be so variable and confusing that the condition is difficult to recognize clinically. My own average for incorrect diagnoses of the disease is 100 per cent. I saw some of the patients whose cases were reported by Dr. Davison and Dr. Rabiner, but did not recognize the true nature of the disease in any instance. When the disease occurs early in life, especially in the first part of the third decade and before extrapyramidal manifestations are presented, because of remissions in the clinical course, it is almost invariably thought to be disseminated sclerosis. When the onset is later in life, in the fifth and sixth decades, in persons who present evidences of vascular disease of the brain and cord, the disease is usually incorrectly regarded as vascular encephalomyelopathy. I made this diagnosis in 2 instances. When the disorder begins with mental symptoms before the appearance of evidences of pyramidal and extrapyramidal involvement the condition is usually diagnosed incorrectly as neurosis or as early Alzheimer's or Pick's disease. In many cases the erroneous clinical diagnosis of tumor of the frontal lobe, dementia praecox, dementia paralytica or cerebral arteriosclerosis is made at autopsy. It is worth while bearing in mind the possibility of the disease, because every once in a while one may make a correct diagnosis; by recognizing the condition one may be able to differentiate it from a possible intraspinal or intracranial expanding lesion and save the patient from a useless laminectomy or craniotomy. All in all, the disease is difficult to diagnose clinically. The histopathologic diagnosis rests on a much more solid basis, and there should be little difficulty in recognizing the condition histologically.

Nosologically, until such time as one has definite information as to the etiologic factors in the disease it is probably as well to adhere to Jakob's classification and nomenclature and to designate it as spastic pseudosclerosis. I doubt, however,

whether the term "spastic," which he employed to differentiate it from the other pseudoscleroses, helps much; in some cases it may be impossible to determine clinically whether one is dealing with spasticity due to pyramidal involvement, or with rigidity due to extrapyramidal involvement; in such cases the term "spastic" is not of much aid in conveying the idea that one is dealing with both pyramidal and extrapyramidal involvement. In spite of this objectionable feature, I believe that the designation "spastic pseudoclerosis," although not a good one, especially for teaching purposes, is, for the present at least, as suitable as any other.

Dr. Israel S. Wechsler, New York: As I listened to Dr. Keschner, I admired his ability to say so much and to speak so well on a condition which is rare and not very important. From time to time pathologists describe 1 or 2 instances of a given syndrome, and the clinician must remember cases of a condition which he is not likely to meet once in a decade. Descriptions of such cases abound in the literature. For reasons one does not know, certain parts of the nervous system are selectively affected; a combination of signs and symptoms naturally results, and a label is given the condition. Actually, one is discussing only a congeries of signs, and not a disease entity. Until the cause is known and one learns what the word "degeneration" means, these descriptions, important as they are and grateful as one should be to the pathologists who furnish them, serve little to elucidate the problem. It is probable that this disease is a so-called heredodegenerative condition. What the hereditary factor is, what the word "degeneration" means, what process is operating to pick out certain pathways and leave others are not known. Obviously, that is why one makes so many errors in clinical diagnosis, and why one will continue to confuse one clinical syndrome with another. The pathologic diagnosis, however, does not make the nature of the disease any clearer. The pathologist speaks of an end reaction, in terms of degeneration, which does not throw light on the nature of the process. It is necessary to wait until the pathologist, the chemist, the pharmacologist, the physiologist and the geneticist get togeher and state what the problem really is. Until then one should avoid creating new syndromes and describing a pathologic picture as a special disease. Certainly, two or three cases do not constitute a clinical entity. I fear that, despite the excellent description given by the authors, little has been added to knowledge of the cause, pathogenesis, hereditary factors or nature of the condition in the cases presented.

Dr. Abraham M. Rabiner, New York: My interest in these patients began when I observed 2 of them, a brother and a sister. Were it not for the fact that we were able to correlate the first 3 cases as a clinical group, they could well have been diagnosed independently as instances of multiple sclerosis, postencephalitic parkinsonism or other disease; as a matter of fact, such a diagnosis was made. The disease in the first case was diagnosed in three neurologic clinics of this city—in one as multiple sclerosis, in another as a postencephalitic parkinsonian syndrome and before this society, by Dr. Wechsler, as amyotrophic lateral sclerosis with mental symptoms. I am convinced that pathologically or in the final appearance of a clinical picture one often cannot arrive at a definite diagnosis unless a comprehensive history, with the sequence of events, is available. I am not particularly interested in the designation of spastic pseudosclerosis; it means nothing to me; I am interested in the clinical picture. In each of these 3 cases the disease occurred before the age of 30. I observed the first patient when her condition was advanced. Within a day or two I saw her brother, a young man in whom the condition had just begun and in whom the only abnormal sign was hypertonia of one foot. This hypertonia had features that suggested both pyramidal

and extrapyramidal involvement. The foot showed involuntary movements, and in those dyskinetic muscles there were observed fibrillary twitchings, while a Rossolimo reflex was elicited. One sees here the onset of a disease in which from the first lesions of the central nervous system were widespread, and yet signs were localized in the foot and leg, with involvement of the pyramidal and extrapyramidal systems and the anterior horn cells. This is an unusual picture; yet evaluation of the clinical syndrome observed in the sister and both brothers reveals that the process in all 3 cases began in one lower extremity, and that the clinical picture advanced to that presented here. We are interested not in creating or fostering another pathologic entity or rare disease but in directing attention to a clinical syndrome with widespread involvement of the nervous system and with a definite sequence of events, producing a clinicopathologic picture which should be recognized and differentiated from other more common diseases for which it is often mistaken.

Dr. Henry A. Riley, New York: I wish to discuss this presentation for a moment. I criticize Dr. Davison and Dr. Rabiner not for inventing the term spastic pseudosclerosis, but for perpetuating it. I hold the same opinion as Dr. Wechsler does, and which I thought Dr. Keschner did when he spoke about this nomenclatural designation, which is a mélange of diagnostic terms. One should be much more thoughtful in the use of diagnostic terms and the acceptance or perpetuation of designations of disease than at present. The idea first of naming a disease from a symptomatic characteristic, such as "spastic," then of describing a pathologic factor in the disease by the word "sclerosis" and finally of removing all support from the pathologic foundation by saying it is "false" seems to me indefensible. The clinical and pathologic features which Dr. Davison described showed that sclerosis was present. It should not be called "false" sclerosis. There was sufficient clinical evidence of degeneration and sclerosis in the patient's nervous system to produce widespread and varied clinical manifestations.

This condition is a diffuse involvement not only of the cerebrum but of the basal ganglia and of certain constituents of the spinal cord. It is a condition which has been described much more defensibly by Dr. Keschner as diffuse encephalomyelopathy of apparently unknown origin. I should have felt much better if Dr. Davison and Dr. Rabiner had made a diagnosis of encephalomyelopathy of unknown origin than of spastic pseudosclerosis.

I think one should, when possible, make diagnoses in pathologic terms. One is forced sometimes to make a diagnosis on the basis of clinical manifestations alone; an example that occurs to me is Adie's syndrome, in which one does not know what pathologic changes occur. When there is a condition with known pathologic changes, however, to perpetuate its designation by a mixture of clinical and pathologic terms and then to upset the whole thing by saying that the pathologic picture is false seems to me the height of nomenclatural folly.

Dr. Charles Davison: As Dr. Rabiner has answered some of the questions, I have little to add, except to answer Dr. Riley. When I first described this disorder (*Brain* **55**:247, 1932), I had the courage to call the disease disseminated encephalopathy (corticopallidospinal degeneration). I became discouraged in trying to give it a new name, and this time I presented the material under the old term spastic pseudoclerosis, because the few other cases recorded histopathologically bore the same label; I also feared that the cases I presented here might not be recognized. In my previous presentation I pointed out the fallacy of the term spastic pseudosclerosis.

MYELORADICULONEURITIS WITH CELL-PROTEIN DISSOCIATION

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Guillain, Barré and Strohl,[1] in 1916, were the first to describe a rapidly progressive motor and sensory syndrome with associated "hyperalbuminosis" of the spinal fluid but without pleocytosis. Their observations were made on 2 soldiers, who subsequently made a rapid and uneventful recovery. This syndrome was designated as radiculoneuritis with hyperalbuminosis of the spinal fluid but without increase in cells, and has since often been referred to as the Guillain-Barré syndrome.

Strauss and Rabiner [2] reported 7 cases of myeloradiculitis in Mount Sinai Hospital. In 4 there was no pleocytosis. Protein determinations were not reported. All the patients gave a history of infection of the upper respiratory tract which bore a chronologic relation to the onset of neurologic symptoms. There was no fatality among the cases.

In 1936, Guillain [3] added 10 cases of this syndrome, distinguished by elevated values for spinal fluid "albuminoids." He did not report any fatalities.

McIntyre [4] reported 8 cases, in 1 of which a pathologic study was made. He stressed the similarity to diphtheritic neuritis in 1 of his cases. Others [5] have reported cases of this syndrome or one closely related to it.

Read at a neurologic conference at Bellevue Hospital, Nov. 21, 1939.

From the Neurological Service (Second Division) and the Department of Pathology, Bellevue Hospital.

1. Guillain, G.; Barré, J. A., and Strohl, A.: Bull. et mém. Soc. méd. d. hôp. de Paris **40**:1462, 1916.

2. Strauss, I., and Rabiner, A.: Myeloradiculitis: Clinical Syndrome, with Report of Seven Cases, Arch. Neurol. & Psychiat. **23**:240 (Feb.) 1930.

3. Guillain, G.: Radiculoneuritis with Acellular Hyperalbuminosis of Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **36**:975 (Nov.) 1936.

4. McIntyre, H.: Ohio State M. J. **33**:875, 1937.

5. (*a*) Matheson Commission: Epidemic Encephalitis: Etiology, Epidemiology, Treatment, Third Report, New York, Columbia University Press, 1939, p. 44. (*b*) Fracassi, T.; Garcia, D. E., and Castane Decoud, A.: Rev. argent. de neurol. y psiquiat. **3**:5, 1938. (*c*) Bassoe, P.: Guillain-Barré Syndrome and Related Conditions (Meningoradiculomyelitis and Meningomyeloencephalitis), Arch. Path. **26**:289 (July) 1938.

Recently, we have had occasion to observe in the neurologic wards at Bellevue Hospital 7 patients whose condition resembled the Guillain-Barré syndrome. Incapacitating symptoms brought them to the hospital from one week to four months after an initial feeling of malaise. Five of the patients were male. Two were Negroes; the others were white. The ages ranged from 17 to 65 years. The patients experienced rapid development of motor weakness, more pronounced in the lower extremities, as well as sensory changes of radicular or peripheral distribution. Tendon reflexes were pathologic in all but 1 case; in 2 cases they were completely absent, except for hypoactive triceps jerks; in 3 others there was absence of knee and ankle jerks, and in 1 case only absence of ankle jerks. There was elevation of the spinal fluid protein with normal cell content; elevation in protein was not as marked, however, as Guillain [3] described in his latest report. There was 1 fatality; the patient died of respiratory failure.

The etiologic factor in this syndrome is unknown. Our evidence for an infectious origin is not as strong as that of Strauss and Rabiner,[2] as only 3 of our patients (cases 2, 4 and 5) had an infection of the upper respiratory tract immediately preceding the onset of neurologic symptoms. Other factors, such as a history of rheumatic arthritis at the age of 23 in a patient aged 26 (case 6), were noteworthy. This patient's illness began with numbness of the extremities. One month later there developed sore throat, and marked motor weakness supervened. The patient who died (case 1) had torticollis four days before the onset of neurologic symptoms. Another patient (case 7) presented symptoms three days after a gastrointestinal upset. Only 1 patient (case 3) gave no history of illness preceding the onset of neurologic symptoms.

McIntyre [4] made cultures of the spinal cord of the only patient in his series who died; no virus was recovered. Cultures of the spinal fluid of 2 of our patients (cases 4 and 5) were sterile, a finding which is further suggestive of a noninfectious origin.

The possibility of vitamin deficiency as an etiologic factor was considered. Vitamin C determinations, made on 5 patients, showed a decrease in 3 instances.

Since the prodromal period varied greatly in these cases, examinations of the spinal fluid were made from three weeks to five months after the onset of symptoms. More than one examination of the spinal fluid, however, was made on each patient. Pleocytosis was not found; the total protein figures were never above 300 mg. per hundred cubic centimeters, except in the case of fatal termination in which within three months there was a rise from 100 to 500 mg. per hundred cubic centimeters, with a decrease to 400 mg. per hundred cubic centimeters two months before death.

On the basis of these values for the total protein of the spinal fluid, the condition in our cases should be classified as an abortive form of the syndrome, as lately described by Guillain,[5] or as another syndrome, since he has differentiated this disease on the basis of an extremely high protein content of the spinal fluid (1,000 to 2,000 mg. per hundred cubic centimeters). However, the specificity of the cell-total protein dissociation is not thereby established,[6] since this phenomenon occurs in other nervous diseases, such as tumors of the spinal cord and brain, postdiphtheritic neuritis, cerebrovascular thrombosis,[7] syphilis of the central nervous system and chronic poliomyelitis.[8]

PATHOLOGIC CHANGES

In the case 1 (no. 1) in which autopsy was performed the pathologic changes of marked peripheral neuritis and degeneration of the columns of Goll and Flechsig were significant. In cases reported by de Morsier and Steinmann [9] in which the clinical symptoms were somewhat related, the pathologic lesion was lymphocytic infiltration of the peripheral nerves. Gilpin and his associates [10] reported involvement of the peripheral nerves and the posterior root ganglia, whereas Alajouanine and his co-workers [11] observed changes in the peripheral nerves, posterior root ganglia and meninges. McIntyre [4] reported changes in the anterior horn cells only. Fracassi and his co-workers [5b] noted most marked changes in the spinal ganglia and peripheral nerves, with mild degeneration of the anterior horn cells.

In contrast to our cases are those of rapidly fatal termination described by Kennedy [12] as "infective neuronitis," in which no abnormal changes in the spinal fluid were noted. Pathologically, there was involvement of the posterior ganglia, spinal roots, ventral horn cells and Betz cells. The disease was transferred to monkeys after an incubation period of five to seven weeks. Furthermore, it is obvious that in

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6. The increase in spinal fluid protein does, however, differentiate this syndrome from peripheral neuritis. In a series of 36 cases of peripheral neuritis observed in the neurologic service of Bellevue Hospital, in one third of which the condition was complicated by radiculitis, the spinal fluid protein was normal (20 to 50 mg. per hundred cubic centimeters).

7. Unpublished data.

8. Georgi, F., and Fischer, Ö., in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1935, vol. 7, pt. 1, p. 344.

9. de Morsier, G., and Steinmann, J.: Presse méd. **44**:1890, 1936.

10. Gilpin, S. F.; Moersch, F. P., and Kernohan, J. W.: Polyneuritis: Clinical and Pathologic Study of Special Group of Cases Frequently Referred to as Instances of Neuronitis, Arch. Neurol. & Psychiat. **35**:937 (May) 1936.

11. Alajouanine, T.; Thurel, R.; Hornet, T., and Boudin, G.: Rev. neurol. **65**:681, 1936.

12. Kennedy, F.: Infective Neuronitis, Arch. Neurol. & Psychiat. **2**:621 (Dec.) 1919.

our cases we are not dealing with acute demyelinating encephalomyelitis with increased cellular but no protein response in the spinal fluid, as described by Davison and Brock.[13]

REPORT OF CASES

CASE 1.—I. M., a Negress aged 47, was admitted to Bellevue Hospital on July 21, 1938, complaining of numbness, weakness and muscular tenderness of all four extremities. Her past history was negligible except for influenza, iritis, joint pains and chronic sinusitis. Four months prior to admission she had a "cold," complicated by torticollis. Immediately there followed numbness and weakness of the lower extremities. Later, the upper extremities were similarly involved. She had no chills.

Physical Examination and Course.—The cranial nerves were normal. There was weakness in all extremities, more marked in the lower, with no atrophy. The deep reflexes were diminished, with absence of ankle jerks; the superficial reflexes were normal. Sensation was normal at first, but later a glove and stocking type of diminution developed, with tenderness over the nerve trunks in the lower extremities. This was followed by swelling of the legs, with bilateral foot drop. Appreciation of vibration was poor in the toes. The patient became progressively worse. The deep reflexes disappeared; the feet became completely paralyzed and the hands weaker. Position sense was lost in the feet; contractures developed. The abdominal reflexes remained active. The patient became incontinent of stool. Complete paralysis of the legs and partial paralysis of the arms developed. Respiratory distress supervened. The temperature, which had been normal, rose to 103 F., and the patient died, ten months after the onset of the illness.

Laboratory Data.—The urine contained occasional red and white blood cells.

Blood examination revealed 4,100,000 red cells; 82 per cent hemoglobin; 8,200 white cells, with 67 per cent polymorphonuclears; 306 mg. of chlorides, 3 mg. of phosphorus, 31 mg. of nonprotein nitrogen and 100 mg. of sugar, per hundred cubic centimeters. The Wassermann reaction was negative. A culture was sterile.

Spinal Fluid: The Wassermann reaction was negative; the colloidal gold curve was flat.

Protein, Mg.	Cells	Time After Onset, Monthly
300	0	5
500	0	7
400	0	8

Pathoanatomic Changes in the Brain, Spinal Cord and Peripheral Nerves (Dr. Lewis D. Stevenson).—Gross Examination: The vessels at the base of the brain were normal, although smaller and thinner than average. There was slight thickening of the meninges at the base, but no appearance of meningitis over the hemispheres and no cortical atrophy or internal hydrocephalus. Gross examination of the spinal cord revealed the dura to be normal, with perhaps slight thickening of the pia-arachnoid. The radial and sciatic nerves appeared normal.

Microscopic Examination: Staining of the right sciatic nerve for myelin sheaths revealed increased space between the bundles with increase of fat and other connective tissue. Longitudinal sections of the sciatic nerve, stained by the Loyez method for myelin, the Cajal method for neurofibrils, the Hortega method for neuroglia and the Masson trichrome stain for connective tissue, showed entire

13. Davison, C., and Brock, S.: Bull. Neurol. Inst. New York **6**:3, 1937.

absence of myelin sheaths. With the trichrome stain many collagen fibers could be seen within the nerve bundles, apparently replacing the nerve fibers. The perineurium and endoneurium contained most of the connective tissue. The epi-

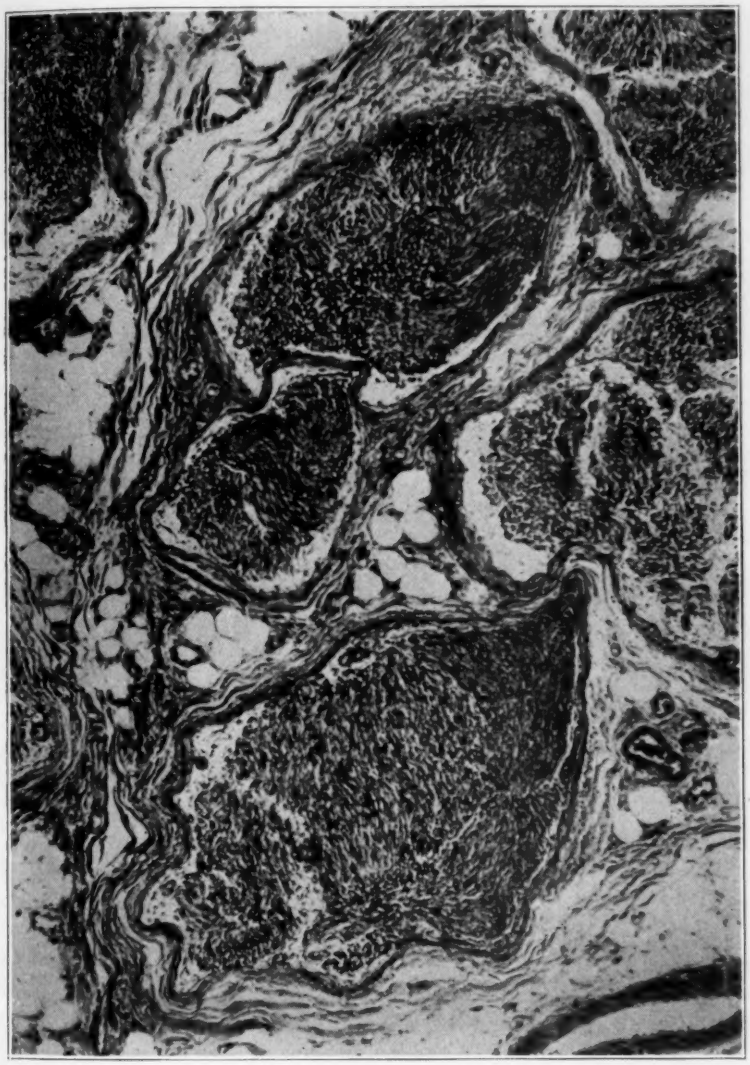

Fig. 1.—Cross section of the right sciatic nerve, stained by Loyez method for myelin sheaths. Abnormal nerve bundles with irregular outlines, in many places concave, are seen instead of those with normal regular convex outlines. The nerve bundles stain lightly because no myelin is present.

neurium contained a great deal of fat. There was no evidence of inflammatory exudate. Sections stained by Cajal's method for neurofibrils were somewhat difficult to interpret because there were abundant fine fibrils which might be

called neurofibrils at first glance, but which were more irregular and probably represented collagen as seen with the trichrome stain. Neurilemma nuclei were abundant. Longitudinal sections stained with sudan III revealed a large amount of

Fig. 2.—Longitudinal section of the sciatic nerve, stained with hematoxylin and sudan III, showing a large amount of fat in free globules and within phagocytes.

fat both in the form of free, round globules and within phagocytes. The right radial nerve showed changes similar to those in the sciatic nerve, but to a lesser degree. In this nerve, however, there was more increase in the endoneurium.

The trichrome and myelin sheath stains of the optic nerves and the trichrome stain of the olfactory bulb and the third and sixth cranial nerves gave normal results.

Myelin sheath and Nissl stains of the lower lumbar region of the spinal cord showed some increase of fibrous tissue in the columns of Goll and some hemorrhage in one posterior horn. The anterior horn cells were fairly well preserved. There appeared to be edema of the myelin sheaths in most columns of the white matter. Sections through the upper lumbar region of the spinal cord showed few anterior horn cells. Examination of the spinal cord in the thoracic region showed definite degeneration of myelin sheaths in the column of Goll (fasciculus gracilis), as illustrated in figure 3. In this section some destruction of the myelin sheaths was also evident in the spinocerebellar pathways, particularly in the dorsal spinocerebellar tracts. The cornucommissural zone of the posterior columns also

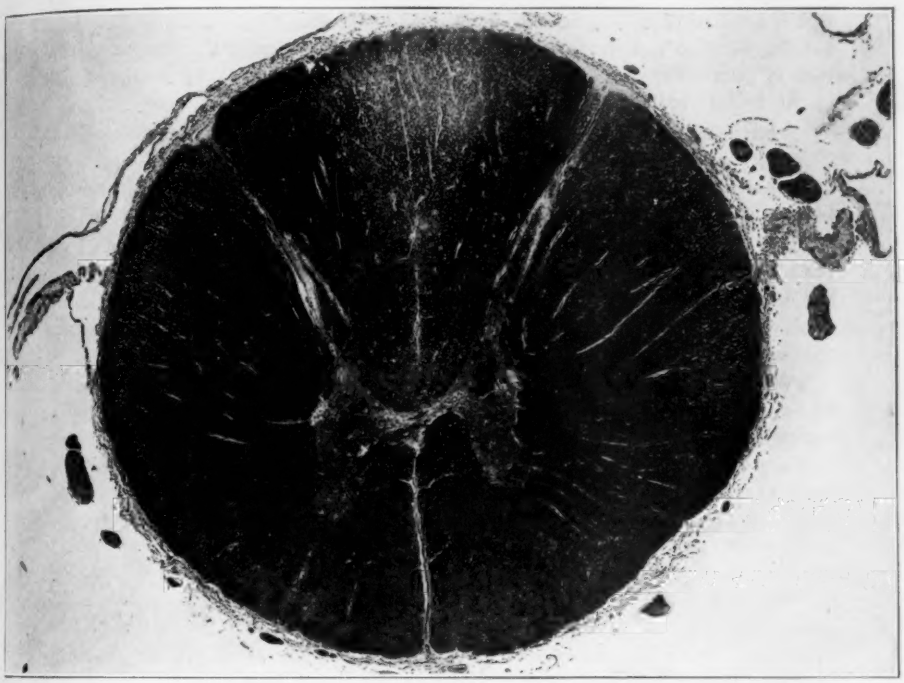

Fig. 3.—Section of the thoracic region stained by the Loyez method for myelin sheaths. Definite degeneration of myelin sheaths in the columns of Goll (fasciculus gracilis) and some destruction of the myelin sheaths in the dorsal spinocerebellar tracts are shown.

showed degeneration. With trichrome, cresyl-violet and Cajal stains for nerve cells and fibrils, few cells were seen in Clarke's column.

Trichrome stains of the midolivary region of the medulla showed the nuclei in the floor of the fourth ventricle to be normal. The pyramidal tracts and other structures appeared normal. Trichrome stains of sections through the middle of the pons revealed no evidence of inflammatory lesions or other pathologic changes in the meninges or the pons. The trichrome and the combined myelin sheath and Nissl stains of the dentate nucleus and cerebellar folia showed no pathologic changes. Trichrome and myelin sheath stains of the midbrain revealed no abnormalities. Trichrome stains of the mamillary bodies gave normal results except

for perivascular edema and a petechial hemorrhage on the lateral margin of one mamillary body. Trichrome and myelin sheath stains of the lenticular nucleus revealed no pathologic changes. Trichrome stains of the tip of the temporal lobe gave normal results. Trichrome stains of the frontal pole showed no abnormality in the meninges or in the brain substance, except small hemorrhagic areas in the gray matter of the cortex.

Microscopic Diagnosis.—There was no evidence of an acute inflammatory lesion in the peripheral or cranial nerves or in any part of the brain examined. There were marked parenchymatous peripheral neuritis, especially in the sciatic nerve, and degeneration of the columns of Goll and Flechsig. It has been suggested by Langworthy[14] (page 301) that the spinocerebellar pathway may originate in the small cells of the sensory ganglia of the spinal cord. This might explain the degeneration in the spinocerebellar tract in our case, since there was degeneration of practically all the motor and sensory neurons reaching the lower part of the spinal cord.

General Autopsy Observations (Drs. Yongue, Silverman and Klemann).—There were slight congestion of the bases of both lungs, which on microscopic examination appeared to be confluent lobular pneumonia; slight myocardial fibrosis; congestion of the spleen, and slight congestion of the adrenal glands.

CASE 2.—A. B., a woman aged 65, was admitted to Bellevue Hospital one week after suffering from a "cold." She complained of numbness in the back and in the lower extremities, associated with chills and fever. Paresthesias and weakness developed in both legs. One month later her hands became weak and numb and her toes tender.

Physical Examination.—The findings were enlargement of the left lobe of the thyroid gland; enlargement of the heart, with a systolic murmur over the aorta; increase in size of the left pupil; poor convergence; slight deviation of the tongue to the right; inability to stand or walk; marked weakness of the peripheral parts of all extremities, with atrophy of the left forearm and hand and both legs; diminution in tone and absence of all reflexes; diminution of touch, pain and temperature appreciation below the knees and in the left hand; absence of appreciation of vibration below the knees and the left elbow; increased tenderness to deep pressure in all extremities, and a considerable amount of pain in the hands and feet.

Course.—After an illness of eleven months, the patient improved gradually. During the next two months of her stay in the hospital she became able to feed herself and to walk. Temperature was always normal. A rhythmic tremor of the left hand developed shortly before she was discharged.

Laboratory Data.—Blood: Examination revealed 4,000,000 red cells; 58 per cent hemoglobin; 32 mg. of nonprotein nitrogen per hundred cubic centimeters, and a negative Wassermann reaction.

Spinal Fluid: The colloidal gold curve was 0000011100, and the Wassermann reaction was negative.

Protein, Mg.	Cells	Initial Pressure, Mm.	Dynamics	Time After Onset, Months
90	..	..	..	2
105	..	55	Normal	3
100+	4	..	..	6
100+	4	..	..	7
140+	2	..	..	9

14. Langworthy, O. R.: Brain **54**:291, 1931.

The Denis-Ayer method revealed 129 mg. of protein per hundred cubic centimeters; the Kjeldahl method, 110 mg.; the cholesterol content was increased to three and four times the normal value; the titrated fatty acid content was 0.2 milliequivalent.[15]

CASE 3.—B. H., a Negro aged 45, was admitted to Bellevue Hospital on July 27, 1939, complaining of weakness and paresthesias of the arms and legs. He gave a history of constipation for ten years previously and of poor appetite for the last two years. One week before admission he noticed weakness in both legs. Several days later the left leg became numb and there were pains in the right side of the neck and shoulder. The weakness progressed, and paresthesias developed in the right arm and both legs, followed by retention of urine.

Physical Examination.—There were weakness, loss of tone and muscular atrophy of the legs and the right arm, more marked peripherally. The biceps, triceps and radial reflexes were increased on the right, but the abdominal reflexes and knee and ankle jerks were absent. All modalities of sensation were diminished in a patchy manner below the fourth thoracic segment on the right and the sixth thoracic segment on the left.

Course.—Nicotinic acid and vitamin B_1 therapy was instituted. After two weeks, bladder function returned; infection of the urinary tract developed. The patient improved enough to sit in a chair six months after the onset of symptoms.

Laboratory Data.—The urine contained clumps of white blood cells.

Blood: Examination revealed 4,900,000 red cells; 13 Gm. of hemoglobin; 9,600 white cells, with 63 per cent polymorphonuclears per cubic millimeter; 120 mg. of sugar per hundred cubic centimeters and a negative Wassermann reaction.

Spinal Fluid: The fluid was clear and colorless, with normal dynamics; the Pandy reaction was + 3; the total protein content 90 to 100 mg. per hundred cubic centimeters; the Wassermann reaction negative, and the colloidal gold curve 1233442121.

CASE 4.—C. L., a man aged 22, was admitted to Bellevue Hospital on Sept. 24, 1938, complaining of pain in the back of the neck, which radiated down to the shoulders. The patient had had gonorrhea seven years before. In July 1939 he had a stiff neck, followed by a "cold" two weeks later. Then for a period of twelve hours he experienced numbness of the arms, trunk and genitalia, with sparing of the legs and head. This episode was accompanied by difficulty in urination.

Physical Examination.—There were slight tenderness of the lower cervical region of the spine and slight weakness of the upper extremities. The biceps, radial and abdominal reflexes were diminished, but the knee and ankle jerks were hyperactive and the plantar reflexes were normal. Sensory appreciation was normal.

Course.—The temperature remained normal, and the patient was discharged, free from symptoms, four months after the onset of the illness.

Laboratory Data.—The urine was normal.

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15. Determinations were made by Dr. Evelyn B. Man, laboratory of biochemistry of the department of psychiatry, Yale University School of Medicine. Brown, W. T.; Gildea, E. F., and Man, E. B.: Lipoids and Proteins Obtained from Approximately Complete Drainage of the Cerebrospinal System, Arch. Neurol. & Psychiat. **42**:260 (Aug.) 1939.

Blood: Examination revealed 4,000,000 red cells; 92 per cent hemoglobin; 12,000 white cells, with 84 per cent polymorphonuclears; a negative Wassermann reaction; 80 mg. of sugar, and 32 mg. of nonprotein nitrogen, per hundred cubic centimeters.

Spinal Fluid: The colloidal gold curve at the end of one and one-half months was 0011223320.

Sugar, Mg.	Protein, Mg.	Cells	Pandy Reaction	Wassermann Reaction	Dynamics	Time After Onset, Mo.
..	125	0	1+	Negative	.....	1½
75	220	8	...	.....	Normal	2

Case 5.—A. S., a white boy aged 17, was transferred to Bellevue Hospital on March 10, 1938, with paralysis of all muscles supplied by the spinal nerves. There was a history of diphtheria, chickenpox and joint pains at the age of 12. An infection of the upper respiratory tract developed in December 1937, followed by temporary pains in the arms and legs. Progressive weakness of all the spinal musculature followed. Within two weeks after the infection artificial respiration was instituted.

Physical Examination.—The cranial nerves were normal. There were marked weakness and atrophy of the intercostal muscles and extremities. The tendon reflexes were absent, and tenderness of the nerve trunks was present. Position and vibration sensibility was lost in the lower and diminished in the upper extremities. Superficial sensation was diminished from the second lumbar to the second sacral segment on the right.

Course.—Four months after the onset the reflexes became normal and superficial sensation returned, but diminished position and vibration sensibility and nerve tenderness persisted. The patient was able to walk two months later. His temperature was not elevated.

Laboratory Data.—The urine was normal.

Blood: Examination revealed 4,000,000 red cells; 40 per cent hemoglobin; 9,000 white cells, with 70 per cent polymorphonuclears; a negative Wassermann reaction; 34 mg. of nonprotein nitrogen, and 84 mg. of sugar, per hundred cubic centimeters.

Spinal Fluid: The culture was sterile; the Wassermann reaction negative; the dynamics normal, and the fluid slightly xanthrochromic.

Protein, Mg.	Cells	Pandy Reaction	Time After Onset, Mo.	Colloidal Gold Curve
300	1	4+	3	0001123211
200	2	3+	4	.....

Case 6.—H. J., a Negro aged 26, was transferred to Bellevue Hospital on May 6, 1938, complaining of weakness of the extremities. There was a history of rheumatism in the knees in 1935. The present illness began in February 1938 with numbness of the hands and feet. Generalized weakness and pains in the cervical and lumbar regions followed. In March a sore throat developed and was followed by paralysis of the legs, weakness of the arms, incontinence of stool, difficulty in swallowing and talking and diplopia. There was no febrile reaction. By April there was initial return of muscular power of the extremities and control of the bowels, but difficulty in starting urination persisted.

Physical Examination.—The patient was thin and euphoric; the heart was enlarged to the right, with a systolic murmur at the base, and the pulmonic

second sound was greater than the aortic second sound. There was weakness of the masseters and right facial muscles. The tongue deviated to the left. There were weakness of the arms and paralysis of the legs, except for slight movement of the toes. Ataxia and muscular atrophy were also present in the extremities. The knee and ankle jerks were absent. There was tenderness of the calves and forearms. Cervical rigidity and a positive Kernig sign were present bilaterally. Loss of sense of touch had a socklike pattern. Loss of appreciation of pain and position and diminution of appreciation of vibration were present in the legs.

Course.—Sensation returned, and the patient was able to walk five months after the onset of the disease.

Laboratory Data.—The urine was normal.

Blood: Examination revealed 4,000,000 red cells; 90 per cent hemoglobin; 6,900 white cells, with 60 per cent polymorphonuclears; 68 mg. of sugar, 34 mg. of nonprotein nitrogen, and 0.35 mg. of ascorbic acid, per hundred cubic centimeters, and a negative Wassermann reaction.

Spinal Fluid: The results of examination are tabulated.

Protein, Mg.	Cells	Pandy Reaction	Dynamics	Wassermann Reaction	Time After Onset, Mo.
...	4	4+	.....	.....	3*
...	10	3+	.....	.....	3½*
...	15	3+	.....	.....	4*
200	0	...	Normal	Negative	4½

* At Willard Parker Hospital.

The colloidal gold curve was 0112333110.

CASE 7.—E. M., a white man aged 24, was transferred to Bellevue Hospital on April 23, 1939, complaining of weakness of the hands and feet. As a child he had had measles and mumps; he had gonorrhea two years before the onset of the present illness. On Jan. 21, 1939, there was a gastrointestinal attack which lasted four days. This was followed by a dull pain in the calves of both legs; pain radiated to the lower part of the back. Weakness of the lower extremities and occasional twitchings of the muscles of the upper extremities were noticed by the patient.

Physical Examination.—There were marked weakness and atrophy of the hands and feet. The knee jerks were hyperactive, and the ankle jerks were absent. Tenderness was present over the nerve trunks in the calves and thighs. The temperature was normal.

Course.—The patient improved and was discharged five months after the onset of the symptoms.

Laboratory Data.—The urine was normal.

Blood: Examination revealed 5,000,000 red cells; 90 per cent hemoglobin; 9,950 white cells, with 80 per cent polymorphonuclears; 91 mg. of sugar and 31 mg. of nonprotein nitrogen, per hundred cubic centimeters, and a negative Wassermann reaction.

Spinal Fluid: The results of examination are tabulated.

Protein, Mg.	Cells	Pandy Reaction	Wassermann Reaction	Colloidal Gold Curve	Dynamics	Time After Onset, Mo.
178	5	(Cumberland Hospital)		.....	.....	2
45	4	Negative	Negative	0011000000	Normal	3
40	..	.....	.....	.....	.....	5

SUMMARY

Seven cases of a rapidly developing motor and sensory syndrome are presented.

The elevation in total protein associated with a normal cellular content is characteristic of the spinal fluid in these cases and is noteworthy as differing from the usually normal findings in the spinal fluid in the peripheral neuritides.

Six patients improved rapidly.

The pathologic changes in the only fatal case were marked peripheral neuritis and degeneration of the columns of Goll and Flechsig.

VESTIBULAR REACTIVITY IN SCHIZOPHRENIA

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AND
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In a series of papers,[1] Angyal has described a syndrome occurring in a certain form of schizophrenia and consisting essentially of a particular type of dissociation, which has been called "loss of ego reference." An outstanding feature of the syndrome is the constant occurrence of paresthesias: bizarre changes in the experience of the body—a subjective impression of excessive lightness or heaviness, of changes in the size of the body and other distortions of the body image. According to Angyal, these paresthesias are due to changes in the muscle tonus, which become dissociated in conjunction with the dissociation of complex behavior tendencies. The explanation of these paresthesias on the basis of changes in the muscle tonus was supported also by the fact that it was possible to produce experimentally similar changes in the experience of the body in normal subjects by introducing passive changes in muscle tonus. Such experimentally produced experiences differ from the corresponding symptoms of schizophrenic patients only in that the normal subjects always recognize these experiences as illusions, while the schizophrenic patients accept them as reality.

The purpose of the present study was to determine whether the aforementioned changes of muscle tonus are reflected also at the level of the involuntary regulation of muscle tonus. To this end the reactivity of the vestibular apparatus, an important regulator of muscle tonus, has been examined in a number of schizophrenic patients and compared with that in a control group of normal subjects.

In the literature there are occasional reports on abnormalities of vestibular function in schizophrenia. As early as 1921, Pekelský[2] reported 2 cases of catatonic schizophrenia in which there was a transitory

From the Research Service of the Worcester State Hospital.

1. Angyal, A.: The Perceptual Basis of Somatic Delusions in a Case of Schizophrenia, Arch. Neurol. & Psychiat. **34**:270-279 (Aug.) 1935; The Experience of the Body-Self in Schizophrenia, ibid. **35**:1029-1053 (May) 1936; Phenomena Resembling Lilliputian Hallucinations in Schizophrenia, ibid. **36**:34-41 (July) 1936; Disturbances of Activity in a Case of Schizophrenia, ibid. **38**:1047-1054 (Nov.) 1937.

2. Pekelsky, A.: Transitorischer Anystagmus bei Katatonie. Ist der Nystagmus willkürlich unterdrückbar? Rev. v. neuropsychopath. **18**:97-102, 1921; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **26**:291, 1921.

absence of nystagmus in response to vestibular stimulation. Rosenfeld [3] observed spontaneous nystagmus in 4 cases of catatonic schizophrenia. The French authors Claude, Baruk and Aubry [4] studied a group of 13 patients with schizophrenia (4 with the catatonic, 8 with the hebephrenic and 1 with the paranoid type). Of the 4 patients with catatonia, 2 showed absence of nystagmus in response to caloric and galvanic stimulation; the third showed a markedly diminished and the fourth a slightly diminished reaction. In the rest of the group fairly normal reactions were obtained. Joo and von Meduna [5] tested a considerable number of schizophrenic patients for vestibular functions, but they made only a single test on each patient, which, considering the variability of these phenomena in the schizophrenic group, is unsatisfactory. These authors found the vestibular reactivity on the whole diminished in response to both rotatory and caloric stimulation. In contrast to the results of Claude, Baruk and Aubry, Joo and Meduna could not observe any difference in the vestibular reactivity in the various subtypes of schizophrenia, and claimed that the reduction of vestibular response is related to the duration of the illness rather than to the clinical type. Sercl and Vinăr [6] also found no correlation between reduced vestibular reactivity and the clinical subtype of schizophrenia. Löwenbach [7] made a careful investigation of the nystagmus in response to caloric stimulations in 30 cases, mostly instances of the periodic catatonic type. He found a lowering of vestibular reactivity.

Because of the fragmentary, and in some respects contradictory, reports in the literature, it seemed advisable to obtain first hand information on the possible changes of vestibular reactivity in the schizophrenic group in general, and then to investigate the relationship between any changes in this function and the clinical syndrome described by Angyal.

TECHNIC

Fifty-eight male schizophrenic patients and 20 normal persons served as subjects in this investigation. Patients with defective ear drums and with a history of middle ear infection or similar ailments were eliminated. Otherwise, no selec-

3. Rosenfeld, M.: Ueber das Vorkommen von Nystagmus bei Schizophrenie, Deutsche med. Wchnschr. **52**:985-988, 1926.

4. Claude, H.; Baruk, H., and Aubry, M.: Contribution à l'étude de la démence précoce catatonique: Inexcitabilité labyrinthique au cours de la catatonie, Rev. neurol. **1**:976-980, 1927.

5. Joo, B., and von Meduna, L.: Labyrinthreizungsuntersuchungen bei Schizophrenie, Psychiat.-neurol. Wchnschr. **37**:26-29, 1935.

6. Sercl, M., and Vinăr, J.: Lesions of Vestibular Apparatus in Schizophrenia, Časop. lék. česk. **76**:213-218, 1937; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **87**:348-349, 1937.

7. Löwenbach, H.: Messende Untersuchungen über die Erregbarkeit des Zentralnervensystems von Geisteskranken, vor allem von periodisch Katatonen, mit Hilfe quantitativer Vestibularisreizung, Arch. f. Psychiat. **105**:313-323, 1936.

tion was made. The length of the patients' stay in the hospital ranged from 0.03 to 22.7 years, with a mean of 5.3 years (standard deviation ±5.4). The nystagmic reactions to both caloric stimulation and rotation were tested. In accordance with the recommendation of Kobrak,[8] mild stimuli were used. This has, among other things, the advantage that the more disagreeable features of the reaction, such as nausea, vomiting and excessive dizziness, do not occur, although the nystagmic movements of the eye are sufficiently marked and fairly numerous. Thus, this method is better suited for quantitative work than is more drastic stimulation.

Caloric stimulation was given in the following way. The patient was placed in a sitting position and his head was tilted forward at a 15 degree angle. Twenty cubic centimeters of water at a temperature of 20 C. was injected into the right ear during a period of ten seconds. The ear was then dried. Sixty seconds after the injection of water the subject's head was quickly tilted backward at an angle of about 90 degrees, and the number of nystagmic beats was counted. The first nystagmic beat appears usually after a latent period of from two to five seconds. The time between the first and the last beat was measured with the aid of a stop watch.

The rotatory stimulation was applied with the aid of a hand driven Bárány chair, 10 revolutions in twenty seconds being used as a stimulus. The counting of the number of nystagmic beats and the measuring of time were done as before.

On the normal control subjects, three experiments with caloric and three with rotatory stimulation were made at intervals of 3 or 4 days. On the 58 patients, the same number of tests was made. However, after the completion of three experiments it was obvious that some of the patients had extremely low reactivity, and since we were particularly interested in this group, seven additional experiments with caloric and seven with rotatory stimulation were carried out on each of the 23 patients with markedly reduced reactivity, the total number of experiments for this group being thus raised to ten caloric and ten rotatory stimulations.[9]

The significant variables in this study are the absolute number and the frequency per second of nystagmic beats. The latter variable is obtained by dividing the number of nystagmic beats by the total duration of the response. Thus, for instance, if a subject has 45 beats in ninety seconds, the average frequency is 0.5 beat per second. By this, however, it is not implied that all or most of the nystagmic beats have the same duration in a given experiment. In fact, usually the nystagmic beats succeed each other rapidly in the first part of the reaction, while toward the end they become very slow and occur with a considerable interval between successive beats.

Before we proceed to a discussion of the results, certain errors of technic must be pointed out. In some cases in which the reactivity was very low only a few extremely weak movements of the eyes could be observed, and it is questionable whether these could be counted as true nystagmic beats. Therefore, in instances in which the total reaction consisted of 6 or less feeble or incomplete beats the count was zero. The main source of error in this study is in the measurement of time. Toward the end of the reaction the nystagmic beats may appear as far apart as ten or fifteen seconds, and a few delayed beats may come

8. Kobrak, F.: Zur Frage einer exakten Messbarkeit der Sensibilität des Vestibularapparates, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **105:**132-134, 1920.

9. For the calculation of individual means which will be referred to in the discussion of the results all available readings were used, since separate calculations on the first three readings only yielded almost identical results.

even after a greater interval. It is therefore not possible to stop the watch at exactly the last nystagmic beat, because it is impossible to foretell whether other beats will or will not follow. However, in spite of these errors of technic, the data are reliable enough to demonstrate the important gross features of the reaction. In order to establish the details accurately, certain improvements in the technic will be necessary.

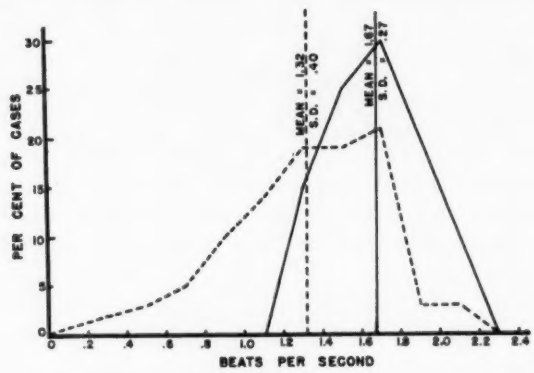

Fig. 1.—Average frequency of nystagmic beats in response to rotatory stimulation (per cent frequency curves of individual means for patients and normal subjects). In this chart and in the accompanying charts, the values for the 58 patients are indicated by a broken line and those for the 20 normal controls by a solid line.

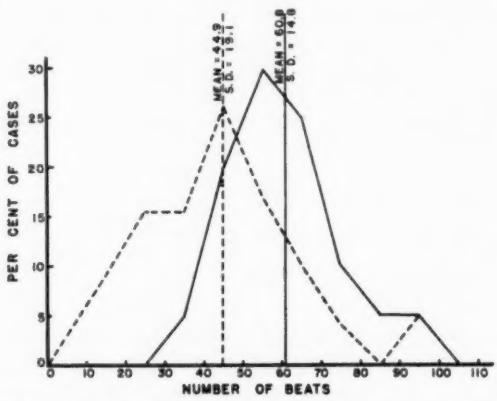

Fig. 2.—Absolute number of nystagmic beats in response to rotatory stimulation (per cent frequency curves of individual means for patients and normal subjects).

RESULTS

There appears to be a marked difference between patients and normal subjects, both in the absolute number and in the frequency of nystagmic beats. The difference was much greater in response to caloric than to rotatory stimulation.

Experiments with Rotatory Stimulation.—Inspection of the curves representing the distribution of patients and normal subjects on the basis of average frequency (fig. 1) and absolute number of nystagmic beats (fig. 2) in the Bárány experiment shows that the nature of the distribution in the two groups is comparable, but that the mean for the patients is significantly lower than that for the normal subjects ($P < 0.01$).[10]

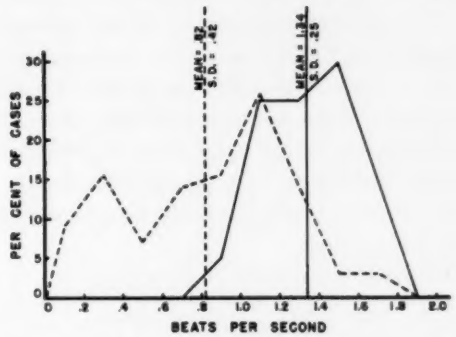

Fig. 3.—Average frequency of nystagmic beats in response to caloric stimulation (per cent frequency curves of individual means for patients and normal subjects).

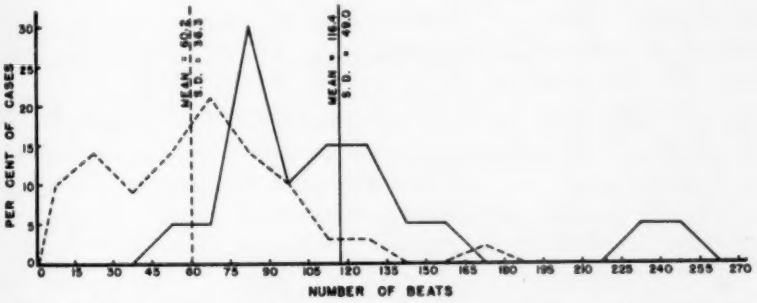

Fig. 4.—Absolute number of nystagmic beats in response to caloric stimulation (per cent frequency curves of individual means for patients and normal subjects).

Experiments with Caloric Stimulation.—The response to caloric stimulation showed a much greater difference between patients and normal subjects than did the reaction to rotatory stimulation.

Graphic representation of the results brings out striking differences in the two groups. Figure 3 represents the distribution of the average frequencies of nystagmic beats. The mean for the patients is 0.82 and for the normal control subjects 1.34 ($P < 0.01$). It will be noted that the values for the normal controls are distributed much more closely about

10. The probability that the difference between patients and normal subjects is due to chance is less than 1 : 100.

the mean than are those for the patients. In addition to the difference of the means, a further sharp differentiation between normal subjects and patients is evidenced by the fact that there is no person in the group of normal controls whose mean value falls below the mean for the patients. As far as we know, in regard to no other physiologic variable has there yet been found such a strong difference between normal persons and schizophrenic patients as a group.

Another striking feature of this curve is that it suggests a tendency toward bimodality, although the number of observations is not sufficient to verify this statistically. In other words, we may have a separate group of patients whose vestibular reactivity is not only lower than that of the normal subjects but much lower even than the average reactivity of the schizophrenic group as a whole. This group with very low reactivity, whose frequency values are between 0 and 0.5, will be considered separately.

The question arises whether the means for the patients and the normal persons differ significantly if the group of patients with the very low values is disregarded. In order to test this we have divided the patients into two groups: Group A comprises patients whose means are above 0.5, and group B, those whose means fall at or below 0.5. These two groups have been compared separately with the normal control group. Even if the patients with the lowest reactivity are disregarded, the mean for the remaining group A (1.01) is still significantly lower ($P < 0.01$) than that for the normal subjects (1.34).

When the absolute number of nystagmic beats is considered, we find differences between patients and normal subjects similar to those with respect to frequency. The difference between the mean for the patients (60.2 beats) and that for normal subjects (116.4 beats) is statistically highly significant ($P < 0.01$).

Dividing the patients into a group with high (A) and a group with low (B) reactivity (see preceding description), we again find that the mean for group A (74.9 beats) remains significantly different ($P < 0.01$) from that for the normal control group (116.4) beats).

Here the question arises whether group A and group B of patients belong to the same or to different populations. In order to obtain a clearcut answer, the number of subjects and the number of experiments must be increased. The question of statistical homogeneity in this connection is, however, one of secondary importance. From our point of view, what is important is the fact that among the schizophrenic patients there is a group with extremely low vestibular reactivity to caloric stimulation and that, as will be seen, the patients belonging to this group tend to have certain clinical characteristics in common.

When the results of the experiments are presented in a somewhat different way, some interesting facts are brought out. We have divided

the patients into four groups according to their degree of vestibular reactivity. The lines of division are not entirely arbitrary, but are suggested by the shape of the respective distribution curves. Group C_1 comprises the patients with the lowest responsivity to caloric stimulation, this is the group which previously has been referred to as group B. Group C_2, the next highest group, comprises patients whose values are higher than those of group C_1 but fall below the mean for the patients. The values for group C_3 fall between the mean for the patients and the mean for the normal subjects. The values for group C_4 are above the mean for the normal subjects. According to the degree of vestibular reactivity to rotatory stimulation, we have similarly divided our subjects into groups R_1, R_2, R_3 and R_4. However, the curves representing the reactions to rotatory stimulation (figs. 1 and 2) do not suggest a separate group with low reactivity. Therefore we have included in group R_1

Frequencies of Varying Degrees of Vestibular Responsivity to Rotatory and Caloric Stimulation in Terms of Absolute Number of Nystagmic Beats

	A. 58 Patients					B. 20 Normal Subjects			
	R_4	R_3	R_2	R_1		R_4	R_3	R_2	R_1
C_4	2	1	..	..	C_4	7	1	..	..
C_3	3	12	10	2	C_3	3	8	1	..
C_2	2	4	4	3	C_2	..	..	..	..
C_1	..	2	2	11	C_1	..	..	..	..

patients whose values are below that of any of the normal controls; subjects with values above these and below the mean for the patients are placed in group R_2; those with values between the mean for the patients and that for the normal subject in R_3, and those with values above the mean for the normal subjects, in group R_4. In A of the accompanying table a two way classification of the patients, based on their vestibular reaction to caloric and to rotatory stimulation, respectively, is given. A similar classification, B, has been constructed for the normal controls. The variable on which classifications A and B are based is the absolute number of nystagmic beats; however, when the frequency is taken as a variable the distribution remains fairly similar. When the data are represented in this way, the difference between the patients and the normal controls is striking. All normal controls fall in the left upper quadrant of the table (blocks C_3R_3, C_3R_4, C_4R_3 and C_4R_4), with 1 exception, which falls into block C_3R_2. The patients, on the other hand, are distributed from the lowest block (C_1R_1) to the highest (C_4R_4). The only block which is well represented by both normal subjects and patients is C_3R_3. However, more than half of the patients fall below this level. There are 11 patients who had an extremely low vestibular

reactivity to both caloric and rotatory stimulation, and hence they fall in the block C_1R_1.

RELATION BETWEEN VESTIBULAR REACTIVITY AND OTHER FEATURES OF THE CLINICAL PICTURE

On the basis of the data presented a marked lowering of vestibular reactivity in the schizophrenic group has been established. Our present material gives leads for further inquiry, but does not as yet afford sufficient grounds for a safe interpretation of this fact. Further studies are being projected with the aim of reaching a better understanding of this peculiarity of the schizophrenic group. We have found, however, some interesting relations between the degree of lowered vestibular reactivity and the clinical picture which may prove to be important clues to the mechanism and the causal factors involved in the reduced vestibular reactivity in the schizophrenic group.

In the investigation of any phenomenon it seems wise to turn one's attention first to cases in which the phenomenon in question appears most conspicuously, and then to extend the work to cases in which it is less marked or is transitional or doubtful. The most pronounced lowering of vestibular reactivity was exhibited by the 11 patients who fall in block C_1R_1 (table A). At this juncture it may be recalled that the present study was undertaken primarily with the purpose of determining whether the syndrome described by Angyal is or is not associated with disturbance of tonus regulation. Among our 58 patients there were 5 who exhibited the syndrome in a clearcut fashion. Four of these were the same patients whose cases Angyal used in his articles as best illustrating the syndrome presented. The fifth patient has only recently been admitted to the hospital. It was interesting to find that all these patients fall in the group with lowest vestibular reactivity. Four of the patients belong to group C_1R_1. The fifth patient's response to caloric stimulation was not quite as low as that of the rest of the C_1R_1 group and fell within the range of C_2. His reaction to rotatory stimulation was, however, lower than that of any other patient of that group. This result fully justifies our suspicion that the abnormalities of muscle tonus which have been claimed to be present in cases of this syndrome are reflected also at the level of the regulation of vestibular tonus.

In spite of the small number of cases, one may safely state that the syndrome described by Angyal is associated with a remarkable diminution of vestibular reactivity. On the other hand, the presence of the syndrome cannot be inferred on the basis of strongly reduced vestibular reactivity in a schizophrenic patient, because in addition to the 5 cases of the syndrome, 6 cases in which the syndrome was absent are also included in group C_1R_1. In 4 of these cases a striking similarity in the clinical

pictures was shown. They were characterized by an extreme degree of apathy, indifference, lack of initiative and poverty of mental content. Although these features are not rare in deteriorated schizophrenic patients, the extreme degree of these symptoms is what characterized this group. A fifth patient may possibly also be classified in this group. The clinical course in his case shows a definite periodicity. He lapses into a stupor for a few weeks; his condition then clears, and he is as nearly normal as before. After a varying period he again passes into stupor. He describes in retrospect his mental state during the stuporous period as one in which he is entirely indifferent to what happens around or to him, that on such occasions he is lacking in energy and the desire to make the least effort, and that during such periods his mind is "blank." In other words, during the stupor his mental state seems to be similar to that of the 4 patients previously referred to. At the beginning of this study he was in a stupor. Then his mental condition began to clear, but before it became as good as on previous occasions he again relapsed into a rather deep stupor. His vestibular reactivity closely followed the clinical course as reflected in the variability in frequency of nystagmic beats in response to caloric stimulation. The first three readings, taken during the first stuporous period, were: 0, 0.18 and 0.19 beats per second. At the time of the fourth reading, which was 0.35 beats per second, the stupor began to clear gradually. The readings during relative clarity were 0.48, 0.71 and 0.52 beats per second. The last reading marked the beginning of the second stuporous period. The successive three readings taken during the second period of stupor were all zero.

The remaining case of group C_1R_1 does not fit into either of the aforementioned groups. It is a fairly typical case of catatonic schizophrenia.

In regard to the correlation between reduced vestibular reactivity and the clinical picture, we have found that the group of cases in which the reactivity is lowest is composed of two types: (1) cases of the syndrome described by Angyal, and (2) cases in which the clinical picture is characterized by an extreme degree of apathy, indifference, lack of initiative and poverty of mental content.

We did not find any definite correlation between the degree of diminished vestibular reactivity, on the one hand, and the conventional subtypes of schizophrenia or the duration of hospitalization, on the other.

SUMMARY

The vestibular reactivity to caloric and rotatory stimulation in 58 unselected male schizophrenic patients and in 20 normal controls has been studied. The caloric stimuli consisted of the injection into the ear of 20 cc. of water at a temperature of 20 C. during a period of ten

seconds, and the rotatory stimuli of 10 turns in a Bárány chair during a period of twenty seconds. The variables studied were the absolute number and the average frequency of nystagmic beat $\frac{\text{(number of nystagmic beats)}}{\text{(total duration of reaction)}}$.

The response of the patients to rotatory stimulation was significantly lower than that of the normal controls, the mean of the number of nystagmic beats being 44.9 and 60.8, respectively, and the mean of the frequencies 1.32 and 1.68, respectively.

In response to caloric stimulation the difference between the patients and the normal controls was even greater, the mean values for the absolute number of nystagmic beats being 60.2 and 116.4, respectively, and the means for the frequencies 0.82 and 1.34, respectively.

In the experiments with caloric stimulation it was found that in the total group of schizophrenic patients whose vestibular reactivity was generally reduced there was a separate group with particularly low responsivity.

We studied the clinical picture of the patients whose reactivity to both caloric and rotatory stimulation was most reduced, and found: (*a*) that all the patients with the syndrome described previously by Angyal (5 in all) fell into this group exhibiting low reactivity; (*b*) that most of the other members of this group were characterized by an extreme degree of apathy, indifference, lack of initiative and poverty of mental content, and (*c*) that in the case of a patient with a periodic course alternating between stupor and periods relatively free from symptoms there was considerable parallelism between vestibular reactivity and the clinical state.

The degree of reduction of the vestibular reactivity was not correlated with the duration of hospitalization or with the conventional subtypes of schizophrenia.

SPECIAL ARTICLES

PHYSIOLOGIC ASPECTS OF SCHIZOPHRENIC WITHDRAWAL

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So far as theoretic orientation is concerned, exclusively "psychogenic" or exclusively "organogenic" attitudes in psychiatry are definitely on the decrease. While American psychiatry, in particular, is broad minded enough to acknowledge the significance of interacting organic, psychologic and social factors in the genesis and the perpetuation of mental disorders, nevertheless much remains to be done in the synthesis of facts of apparently different orders that are obtained by the use of the technics of the physiologist, the psychologist and the sociologist, respectively. So great are the methodologic difficulties that it is to be feared that many workers, consciously or otherwise, don mental blinders as a defense against the complexities of the problems. Thus, while admitting the desirability and even the necessity of a synthetic approach, they too often carry on their individual studies in a single domain to the practical exclusion of attention to other domains.

To a considerable extent the unilateral approaches can be justified as means of bringing to bear special varieties of technical competence. Nevertheless, the meaning of such partial findings is likely to be mostly lost except as the data are successfully embodied in the larger whole. The inner unity—the connectedness—of the phenomena must somehow be found and reflected in the appraisal of the net meaning of the data. The outstanding task of psychiatry today is to evolve a methodology for such syntheses. A step toward this end is to recognize parallel or common meanings in the data derived from different approaches. In this paper we wish to point out what seems to us a rather meaningful connection between certain features in the psychology and the physiology of schizophrenia.

It is generally recognized that in spite of the great variety of clinical pictures in the schizophrenic group of disorders, one symptom is common to all of them. This is the schizophrenic withdrawal. Psychologically,

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withdrawal means that the vital relations between a person and his physical and social environment become less intense and less numerous. Since life processes consist of interactions between the person and his environment, the consequence of a partial break in environmental contacts leads to an impoverishment and diminished intensity of living. This aspect of schizophrenic withdrawal is expressed psychologically in lack of interest, apathy and indifference. However, the life of the schizophrenic person runs at a low ebb not only psychologically but also physiologically. This is manifested in a lowering of the basal levels of various physiologic functions, such as the basal oxygen consumption rate, basal blood pressure and circulation time.

The lessening of interaction between the person and his environment in schizophrenia becomes particularly evident when he is exposed to the influence of various stimuli. The reduction of responses to stimuli emanating from the physical and social environment is well known in the psychology of schizophrenia. We wish to present evidence that a diminution of responsiveness is paralleled also in the physiology of schizophrenia. This may be illustrated by certain findings obtained in our laboratories.

Our data thus far obtained on the physiologic hyporeactivity of the schizophrenic patient pertain to three major fields: general metabolism, functions of the autonomic nervous system and functions of the central nervous system.

Hyporeactivity to Metabolic Stimulants.—The response of the schizophrenic organism to metabolic stimulation is less than normal, so that to induce a comparable reaction excessive doses are necessary. In a therapeutic experiment, Hoskins and Sleeper [1] administered as much as 48 grains (3 Gm.) daily of desiccated thyroid substance to a patient with little apparent physiologic reaction. Following this lead, Cohen and Fierman [2] administered thyroid to 8 schizophrenic patients in doses of 15 to 18 grains (1 to 1.2 Gm.) daily for several months. Despite an increase in the oxygen consumption rate from a premedication level of 95 to 141 per cent of prediction, the pulse rate tended to decrease once a maximal level of 110 had been reached. No ill effects from the large doses of thyroid were observed. No excessive perspiration, tremor or gastrointestinal disturbance was noted. The psychiatric-clinical changes observed during the period of hyperthyroidism were slight.[3]

1. Hoskins, R. G., and Sleeper, F. H.: A Case of Hebephrenic Dementia Praecox with Marked Improvement Under Thyroid Treatment, Endocrinology **13**:459, 1929.

2. Cohen, L. H., and Fierman, J. H.: Metabolic, Cardiovascular, and Biochemical Changes Associated with Experimentally Induced Hyperthyroidism in Schizophrenia, Endocrinology **22**:548, 1938.

3. Cohen, L. H.: Psychiatric Changes Associated with Induced Hyperthyroidism in Schizophrenia, Psychosom. Med. **1**:414, 1939.

The reduced metabolic reactivity is not restricted to a specific endocrine substance but is present also on administration of dinitrophenol, which is a general oxidative stimulant. After the administration of 300 mg. of dinitrophenol to 20 schizophrenic patients and a comparable number of normal controls, Freeman [4] found that the response in cutaneous temperature, insensible perspiration rate and oxygen consumption rate was less in the patients.

Hyporeactivity of the Autonomic Nervous System.—A lessened degree of reactivity was also noted in the field of autonomic physiology. The increase in blood pressure and pulse rate induced by the intravenous administration of 0.05 mg. of epinephrine hydrochloride was definitely less in schizophrenic patients than in normal subjects.[5]

Marked differences in autonomic responsiveness between schizophrenic and normal persons were found by Freeman and Rodnick.[6] These investigators induced experimentally a rather severe stress situation by having the subjects breathe hot moist oxygen, thus blocking the loss of heat from the lungs. They found that the response in blood pressure, heart rate and respiratory volume was markedly less in schizophrenic patients than in normal subjects. The reaction to this stress situation was in more than one fourth of the normal controls so alarming that the experiment could not be completed, while the patients gave little sign of any discomfort.

Hyporeactivity of the Central Nervous System.—A depression of reactivity referable to the central nervous system was found by Angyal and Blackman,[7] who studied the nystagmic response to vestibular stimulation in 20 normal and 58 schizophrenic subjects. Both caloric and rotatory stimulations were applied. The variables which they studied were the absolute number and the frequency of nystagmic beats, $\frac{\text{(number of nystagmic beats)}}{\text{(total duration of reaction)}}$. In response to rotatory stimulation they found a 21 per cent reduction in the absolute number and a 26.2 per cent reduction in the frequency of nystagmic beats. In response to caloric stimulation the schizophrenic patients showed a 38.8 per cent reduction

4. Freeman, H.: Heat-Regulatory Mechanisms in Normal and Schizophrenic Subjects Under Basal Conditions and After the Administration of Dinitrophenol, Arch. Neurol. & Psychiat. **43**:456 (March) 1940.

5. Freeman, H., and Carmichael, H. T.: A Pharmacodynamic Investigation of the Autonomic Nervous System in Schizophrenia: I. Effect of Intravenous Injections of Epinephrine on the Blood Pressure and Pulse Rate, Arch. Neurol. & Psychiat. **33**:342 (Feb.) 1935.

6. Freeman, H., and Rodnick, E. H.: Autonomic and Respiratory Responses of Schizophrenic and Normal Subjects to Changes of Intra-Pulmonary Atmosphere, Psychosom. Med. **2**:101 (April) 1940.

7. Angyal, A., and Blackman, N.: Vestibular Reactivity in Schizophrenia, Arch. Neurol. & Psychiat., this issue, p. 611.

in the frequency and a 48.3 per cent reduction in the absolute number of nystagmic beats.

The results of a recent study by Rodnick [8] also indicated a diminished responsivity of the central nervous system. He studied the difference of response in cutaneous resistance in schizophrenic and in normal subjects. The response to a strong auditory stimulus did not differ to any great extent in the two groups. The preparatory response of the patients to the "ready" signal, however, was only half that of the normal subjects.

Besides our own data, results obtained by other workers also seem to support our thesis of general reduction of responsiveness in schizophrenic patients. We shall refer only to two such findings. Fischer [9] reported that in 277 cases of schizophrenia the specific dynamic action of protein (increase in basal metabolic rate after ingestion of meat) was diminished.

Meco [10] observed that during treatment with various thermogenic agents, mainly foreign proteins and other chemical substances, the rise in temperature in the schizophrenic group was far below that in other groups, and that the whole "thermic shock" was much diminished in the schizophrenic patients.

SUMMARY

Summarizing, we may say that in schizophrenia a rather general reduction of physiologic responsiveness is present. The reaction to metabolic stimulants, such as thyroid and dinitrophenol, was definitely diminished. The reaction to epinephrine administered intravenously as well as to the blocking of heat loss through the lungs was definitely less in schizophrenic patients than in normal persons, indicating reduction of autonomic responsiveness. The nystagmic response to rotation and to caloric stimulation was greatly diminished. The change in cutaneous resistance in response to a preparatory stimulus was far below the normal.

We are not prepared to state whether psychologic withdrawal is caused by a physiologic withdrawal (hyporeactivity) or vice versa. It is probable that neither is the case, but that one is dealing with withdrawal of the total personality manifested in a variety of psychologic and physiologic characteristics.

8. Rodnick, E. H.: A Comparison of Schizophrenic and Normal Subjects with Respect to Two Measures of Autonomic Reactivity: Weight Loss and Galvanic Skin Response, to be published.

9. Fischer, S.: Gasstoffwechselveränderungen bei Schizophrenen; Bericht über 345 Kranke (277 Schizophrene, 68 Depressive), Ztschr. f. d. ges. Neurol. u. Psychiat. **147**:109, 1933.

10. Meco, O.: L'esistenza e l'interpretazione di una scarsità di reazione piretica nei dementi precoci, Riv. di pat. nerv. **44**:677, 1934.

The question may justly be asked: What value may be derived by bringing together a number of physiologic facts under the common heading of decreased responsiveness and, further, by tying up all these features with psychologic withdrawal? The possible value of such an attempt may be summarized in the following points.

1. It may well be that, for instance, a diminished response to thyroid and a diminished response to vestibular stimulation are distinct phenomena, with no relation at all between them. Furthermore, it is possible that there is only a superficial analogy between those instances of reduced physiologic resistiveness which we have cited and the various psychologic symptoms grouped in the category of withdrawal. On the other hand, it may also be true that there is a significant and meaningful connection between all these features. In other words, it is possible that what is observed in schizophrenia is not resistance to thyroid medication, a lessened response to epinephrine, a diminished vestibular reactivity and psychologic indifference to stimuli of the physical and social environment, but only manifestations of one and the same condition. It may be useful to broaden the concept of withdrawal to designate not a purely psychologic but a "holistic" or "psychobiologic" phenomenon. The possibility that this phenomenon may be holistic and not segmental is strong enough to permit this assumption to be used as a working hypothesis.

2. The type of approach which we are suggesting here should not be a retreat into generalities. On the contrary, we wish to emphasize the necessity of specific and concrete studies. After a number of psychologic and physiologic features are brought together under the common concept of withdrawal, this concept, which is used at present with a somewhat vague and general connotation, gains a new and rather definite meaning. The phenomenon of withdrawal may thus be specifically defined as consisting of such and such psychologic and physiologic characteristics.

3. The assumption of a psychobiologic disturbance, characterized by certain psychologic and physiologic manifestations, raises new problems and gives specific hints for further studies. It makes a distinct difference with regard to the type of problems one investigates whether one works with this or with some other hypothesis. This may be illustrated by a hypothetic example. Once the resistance of the schizophrenic person to thyroid medication is established, one may attempt to study systematically whether this phenomenon is due to (1) disturbed absorption, (2) some chemical agent in the blood which may neutralize thyroxine or (3) tissue resistance. That is, one may study resistance to thyroid as such. This type of investigation is necessary, and it should be made in every instance. However, if one is oriented along

the lines featured, further investigations are also indicated. One not only should study decreased reaction to thyroid as such but also should consider the possibility that this phenomenon is a manifestation of a generalized condition of reduced reactivity. The latter being assumed, the first task will be to determine what functions are involved and to what degree. Our studies already indicate that the reduction of reactivity in persons with schizophrenia is not uniform; one physiologic function undergoes a greater reduction than another; some functions remain unchanged, and in some respects the reactivity may even be increased. The last possibility was suggested, for example, by Freeman and Hoskins'[11] finding of an increased response of the blood pressure to a preparation of adrenal cortex. The increase of blood lipids after testosterone medication observed by Randall[12] might be of the same order. Therefore, the reduction of responsiveness, since it does not involve all functions of the organism uniformly, will probably be most adequately presented in the form of a profile, which would indicate what functions are involved and to what degree. After such a profile has been obtained and the essential psychologic and physiologic components of withdrawal have been defined, one will be better equipped to investigate the causation of this complex phenomenon.

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11. Freeman, H., and Hoskins, R. G.: Comparative Sensitiveness of Schizophrenic and Normal Subjects to Glycerin Extract of Adrenal Cortex, Endocrinology **18**:576, 1934.

12. Randall, L. O.: Effect of Testosteron on Serum Lipids in Schizophrenia, J. Biol. Chem. **133**:137, 1940.

Case Reports

SUBARACHNOID AND INTRACRANIAL HEMORRHAGES DUE TO METRAZOL

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Although the use of metrazol in the treatment of some psychoses and psychoneuroses is of comparatively recent origin, it has already proved of definite value. The literature on its advantages is voluminous and, although metrazol used in convulsive doses theoretically should be associated with a certain degree of danger to life, there have been very few deaths reported from its use. Von Angyal and Gyárfás [1] appear to have published the first report of death from metrazol (see table). Subsequent deaths have been mentioned in articles by Stähli and Briner,[2] Hayman and Brody,[3] Fellows and Koenig [4] and Hassin.[5] Neuropathologic studies on animal experiments have been reported by Stender,[6] Reitmann [7] and Liebert and Weil.[8] The characteristic observations in the brains of animals which died after injections of metrazol were subarachnoid and intracerebral hemorrhages similar to those in the human patient studied by us.

REPORT OF A CASE

History.—A white single woman aged 33 was admitted to the Eastern State Hospital on March 18, 1939, because of psychotic behavior. Her paternal grandfather, four paternal aunts, one paternal cousin, the patient's mother and one brother all at some time displayed psychotic behavior, and most of them had

From the Eastern State Hospital.

1. von Angyal, L., and Gyárfás, K.: Ueber die Cardiazol-Krampfbehandlung der Schizophrenie, Arch. f. Psychiat. **106**:1, 1936.

2. Stähli, R., and Briner, O.: Beitrag zur Krampfbehandlung der Schizophrenie, Ztschr. f. d. ges. Neurol. u. Psychiat. **160**:649, 1938.

3. Hayman, M., and Brody, M. W.: Metrazol Therapy in Schizophrenia, J. A. M. A. **112**:310 (Jan. 28) 1939.

4. Fellows, R. M., and Koenig, F.: A Death Associated with Metrazol Therapy, J. Nerv. & Ment. Dis. **90**:358 (Sept.) 1939.

5. Hassin, G. B.: Cerebral Changes in Fatal Cases Following Treatment with Barbital, Soluble Barbital U. S. P., Insulin and Metrazol, Arch. Neurol. & Psychiat. **42**:679 (Oct.) 1939.

6. Stender, A.: Ueber Provokation epileptiformer Anfälle durch Cardiazol, München. med. Wchnschr. **48**:1894 (Nov. 26) 1937.

7. Reitmann, F.: Zur Frage der zerebralen Veränderungen bei experimentellen Cardiazolvergiftungen, Psychiat.-neurol. Wchnschr. **40**:391 (Aug. 27) 1938.

8. Liebert, E., and Weil, A.: The Histopathology of the Brain Following Metrazol Injections, Elgin State Hosp. Papers **3**:51 (Jan.) 1939.

had to be hospitalized in institutions for patients with mental diseases. The patient was born in the state of Washington, the sixth of eleven siblings, of a normal pregnancy and delivery. Her early development and schooling were not unusual. She was a member of the Christian church but did not attend regularly. She never used alcohol, tobacco or drugs. After completing one year at a college she expressed the desire to work in a business office and was considered efficient and reliable. After one year, however, she preferred to remain at home with her mother and occupied herself with housework. While she was congenial with the family group, she had few friends outside and never displayed any interest in the opposite sex. The menses began at 13 years of age; the periods were regular until 1934, at which time an ovarian cyst was removed surgically. At about the same time she had a period of overactivity, during which she sang, constantly prayed and had crying spells. She was placed in a private sanatorium, where she remained for several months. She improved sufficiently to return

Deaths from Metrazol Reported in the Literature

Case	Authors	Comment
1	Von Angyal and Gyárfás [1]	Sudden death ½ hour after second injection of metrazol due to aortic insufficiency and myocardial degeneration
2	Stähli and Briner [2]	Death due to pulmonary embolism from thrombosed pelvic veins
3	Stähli and Briner [2]	Death 4 hours after fourth injection of metrazol; bilateral hypernephroma and enlarged thyroid at autopsy
4	Hayman and Brody [3]	Death after 6th injection of metrazol; autopsy revealed chronic endocarditis and marked congestion of all organs, including brain
5	Fellows and Koenig [4]	Death after 12th injection of metrazol; autopsy revealed degeneration of cortical cells, swelling of cells of basal ganglia and degeneration of liver cells, with vacuolated cytoplasm
6	Hassin [5]	Death after 2d injection of metrazol (patient had previously received insulin shock therapy); brain showed swelling of ganglion cells, chromatolysis and occasional edema, liquefaction and neuronophagia
7	Roback and Miller (this paper)	Death 24 hours after ninth injection of metrazol; autopsy revealed degeneration of liver, subarachnoid and multiple petechial hemorrhages and marked congestion of brain and other organs

home and adjusted well for about six months, after which time she requested to be sent back to the sanatorium. After a few weeks she was considered to have recovered and returned home. Her behavior was normal until February 1939, two weeks after removal of a second ovarian cyst, when she again became overactive, slept poorly and complained of being nervous. She was given injections of estrone (theelin), with no effect. Since she could not be cared for in a general hospital, commitment to a hospital for mental diseases became necessary. In the hospital she made an extremely poor adjustment. She was noisy and exhibited purposeless, bizarre overactivity, such as clasping her hands before her face, screaming, kneeling and then toppling backward but never falling. She refused to eat, and it was necessary to feed her by tube.

Examination.—She was extremely uncooperative for the purposes of examination and struggled against every procedure. She rarely answered questions correctly, and many of her replies were irrelevant. Her spontaneous conversation was largely filled with recriminations and expressions which indicated a sense of

impending disaster. Her mood varied from extreme excitement to tears in the course of a few minutes. She reacted constantly to auditory hallucinations. Her sensorium could not be accurately determined because of marked confusion and excitement.

Physical examination was incomplete and unsatisfactory, but it revealed large, chronically infected tonsils and a blood pressure of 128 mm. of mercury systolic and 80 mm. diastolic. Laboratory examination showed a value for hemoglobin of 70 per cent. There were 4,370,000 erythrocytes and 6,400 leukocytes per cubic millimeter of blood. Kahn and Kline tests of the blood and of the cerebrospinal fluid gave negative results. The urine on admission was cloudy; the specific gravity was 1.021; the reaction was acid, the test for albumin showed a 1 plus reaction, and a test for sugar gave negative results. Microscopic examination revealed 1 plus hyaline casts, 2 plus pus cells and 3 plus bacteria.

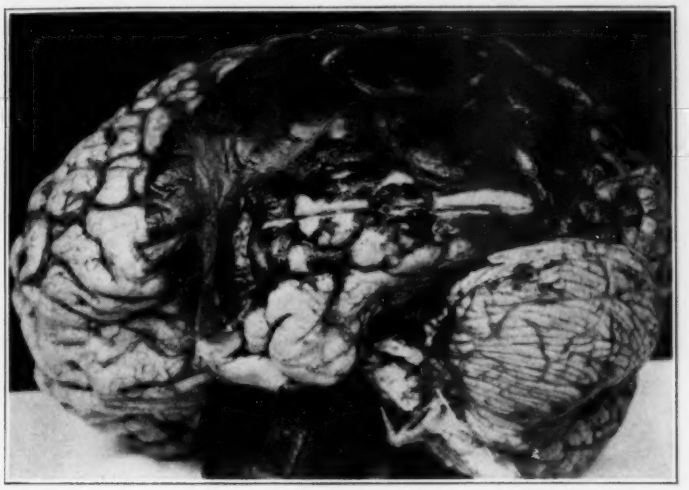

Fig. 1.—Subarachnoid hemorrhage.

Course.—Because of threatened exhaustion from overactivity and failure to respond to the usual sedative and supportive measures, it was decided to give the patient metrazol shock therapy despite the evidence of a pathologic condition of the kidney. Five days after admission to the hospital she was given 4 cc. of metrazol (10 per cent) intravenously; this was not followed by a convulsive reaction. Five minutes later she was given an injection of 5 cc. of metrazol, which was accompanied by a convulsion. Metrazol was administered every other day, three times weekly, and each injection was followed by a satisfactory convulsive reaction.

About twenty-four hours after the ninth injection (5 cc.), the patient suddenly appeared cyanotic, and her pulse was thready. The rectal temperature was 99.4 F.; the pulse rate was 120 per minute, and the respiratory rate was 24. Hypodermoclysis of 1,000 cc. of 5 per cent dextrose in saline solution was given immediately, after which her color and pulse were somewhat improved. However, one-half hour later she again became cyanotic; her pulse was weak and irregular, and respirations were labored. Cardiac stimulants were administered, but the patient

failed to rally, and death ensued about one-half hour later. Clinically, the sequence of events had every appearance of death due to cardiac failure, as there were no objective symptoms referable to the central nervous system.

Necropsy.—Complete necropsy was performed about twenty-two hours after death. The body was moderately well developed but undernourished. The skin was of good color, smooth, moist and elastic. The thorax was narrow, and the mammae were atrophied. There was a thin layer of subcutaneous fat. The lungs showed no pathologic changes. The heart weighed 205 Gm. and was well contracted. The valves were normal, and the cardiac chambers were not distended. The walls of the heart were not thickened. The liver was small, weighing only 820 Gm. The spleen weighed 63 Gm., and both kidneys were reduced in size, especially the right, which weighed 95 Gm. The weight of the pancreas was 45 Gm. There were chronic cystitis, proctitis and cervicitis. Both ovaries and the appendix were absent.

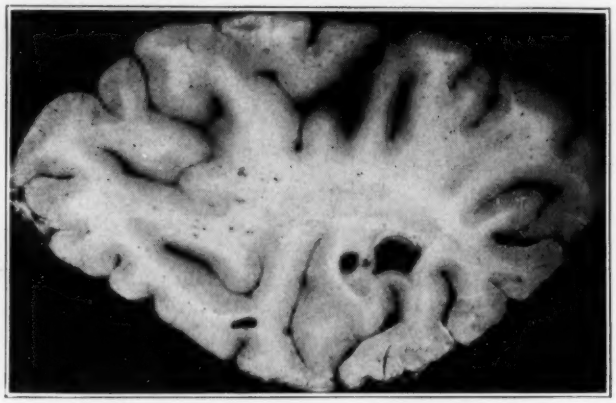

Fig. 2.—Coronal section through the occipital lobe, showing petechial hemorrhages.

Cranium: The cranial contours were normal. The scalp and skull were of medium thickness; the latter was sawed without difficulty. The dura mater was easily separated from the skull. The brain weighed 1,375 Gm. and was markedly congested. There was an extensive subarachnoid hemorrhage over the left frontotemporoparietal region (fig. 1). There was also a subarachnoid collection of blood at the base of the brain, extending from the optic chiasm anteriorly to the cisterna magna posteriorly; the latter was filled with blood. There were several small subarachnoid hemorrhages in various regions of the right cerebral hemisphere. The dural sinuses did not contain any thrombi. The pituitary gland showed no pathologic changes. The brain was fixed in toto in a 10 per cent concentration of solution of formaldehyde U. S. P., after which it was sectioned frontally. Numerous pinhead-sized hemorrhages were present in the white matter of the left and right temporal and parietal lobes and in the splenium of the corpus callosum. There were several somewhat larger hemorrhagic areas in the left hippocampus and in the right occipital lobe, near the posterior horn of the lateral ventricle (fig. 2). The entire cortex was congested, and the numerous pinpoint-sized red areas were thought to be engorged vessels.

Microscopic examination revealed the following observations.

Meninges: In the regions of subarachnoid hemorrhage the meshes of the arachnoid were distended and filled with blood. In several places the blood had penetrated the pia mater, and hemorrhages were seen in the cortical molecular layer. In the nonhemorrhagic areas all blood vessels were dilated and many were engorged. There was an occasional thrombosed vein. The meninges were for the most part edematous, and in many regions numerous phagocytic cells were seen in the arachnoidal interstices.

Cerebral Cortex: Sections from different areas of both hemispheres showed numerous petechial hemorrhages (fig. 3). The hemorrhages were limited to

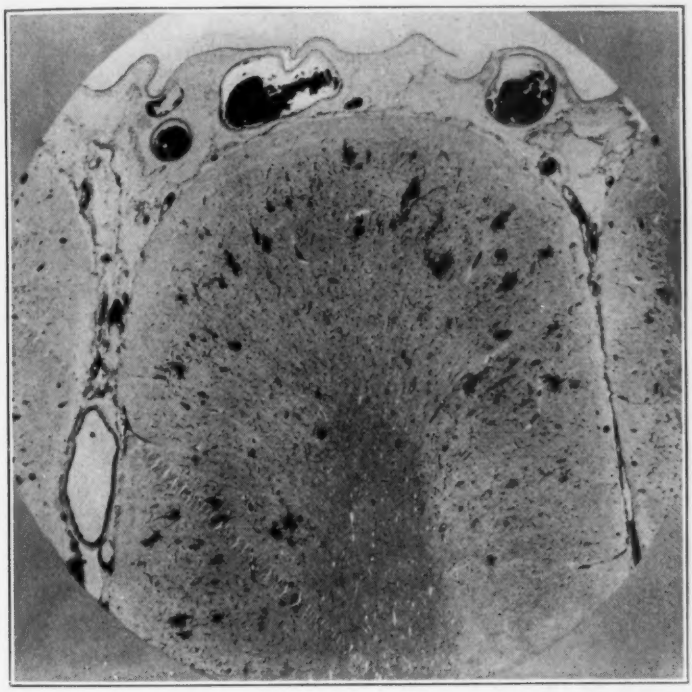

Fig. 3.—Edema of the meninges, with congestion. Note the numerous petechial hemorrhages in the cortex. Heidenhain stain; × 13.

the superficial cortex, and none could be seen in the regions beneath the sulci. In many areas the cortical lamellation was distorted, particularly beneath regions of subarachnoid hemorrhage. Numerous ganglion cells exhibited swelling and chromatolysis; some cells were pyknotic. Neuronophagia, however, was relatively rare. In some areas ganglion cells contained fine particles of black pigment, which probably was blood pigment. Some glia cells were slightly swollen.

Cerebral White Matter: The pericellular spaces were moderately dilated. Many small and larger areas of demyelination were seen (fig. 4), in which fragments of myelin had been retained; all demyelinated areas contained degenerated erythrocytes. Sections stained with scarlet red did not show any fat, and there was

Fig. 4.—Area of demyelination in the white matter of the left parietal lobe. Heidenhain stain; × 35.

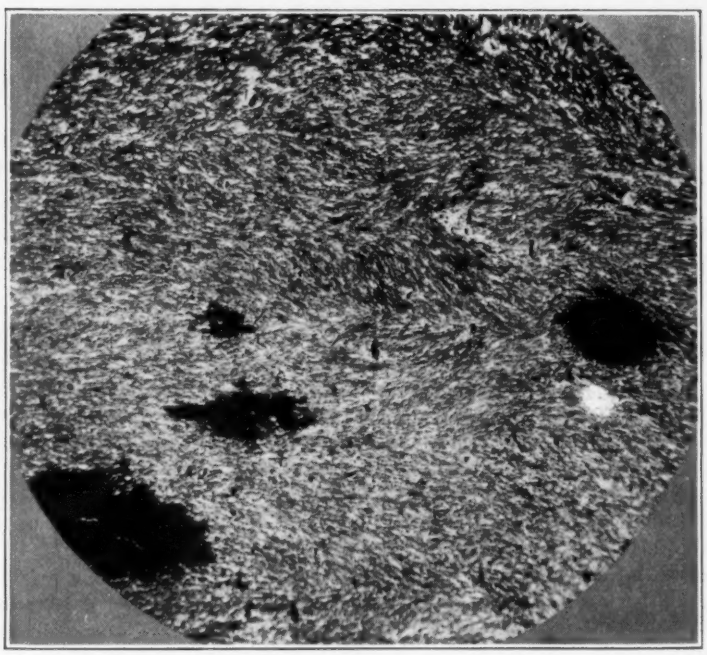

Fig. 5.—Hemorrhages in the splenium of the corpus callosum. Heidenhain stain; × 35.

absence of glial reaction in these areas as well as in their vicinity. Petechial hemorrhages without demyelination were not common except in the splenium of the corpus callosum (fig. 5). In some regions of the white matter a moderate degree of mobilization of glia was seen. The astrocytes and oligodendrogliocytes were slightly swollen.

Hippocampus: The cells showed chromatolysis, pyknosis and considerable neuronophagia. The ganglion cells contained fine particles of black pigment.

Cerebellum: Several petechial hemorrhages were seen in the molecular layer only. The Purkinje cells showed swelling and chromatolysis.

Blood Vessels: All vessels, particularly the capillaries and arterioles, were markedly congested. The endothelium was swollen, and the connective tissue was edematous. There was rarely a lacerated capillary (fig. 6), with blood in the

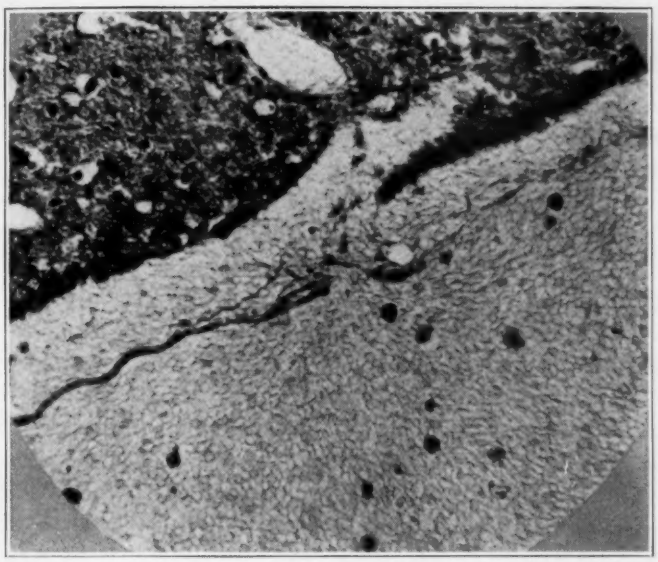

Fig. 6.—Lacerated capillary. Mallory's phosphotungstic acid stain; × 310.

pericapillary space. There was an occasional (rare) collection of lymphocytes in the adventitial space.

Liver: The blood vessels were markedly congested. The liver cells were considerably swollen, and their cytoplasm was markedly vacuolated; many cells had lost the greater part of their cytoplasm. The nucleus of most cells was large.

COMMENT

The advisability of treating this patient with metrazol may be questioned by some in view of the renal pathologic condition as evidenced by the presence of 1 plus reactions for albumin and hyaline casts. However, the patient was overactive and restless and had to be tube fed; the prognosis as to life was extremely poor, as exhaustion appeared

imminent. Therefore, metrazol therapy seemed indicated, with full knowledge of its possible danger. This raises the question of contraindications to treatment with metrazol. Originally, heart disease, renal pathologic change, menstruation and several other conditions were considered contraindications. However, with accumulation of experience and better understanding of the effects of the drug on the body the contraindications have been reduced in number. In our experience, the risk incurred in metrazol therapy is small; this was the only fatality encountered in the treatment of more than 300 patients. We therefore have felt justified occasionally in taking a chance on the remote possibility of a fatal accident, considering this preferable to denying the benefit of metrazol therapy to a patient in whose case the prognosis without the treatment appears poor, even though minor contraindications exist.

The deaths from metrazol of human patients whose cases have been reported in the literature so far are listed in the table. Unfortunately, some of these lack complete histopathologic studies. Hassin [5] observed swelling of the ganglion cells, chromatolysis, occasional edema, liquefaction and neuronophagia, changes which do not differ from those observed in cases of poisoning by other drugs. In our case, as in that reported by Fellows and Koenig,[4] there was considerable degeneration of the liver cells. Although the pathologic process may have antedated the treatment with metrazol, it is also probable that the degenerating process was enhanced by the metrazol. We believe that the hepatic disease bore a definite relation to the subarachnoid and petechial hemorrhages in the brain. We do not think that metrazol alone in the small doses which this patient received is sufficiently toxic to have increased the permeability of the cerebral vessel walls or to lacerate small vessels (fig. 6). According to Liebert and Weil,[9] hyperemia follows an initial sudden contraction of the cerebral arteries after an injection of metrazol, but no mention is made of the duration of the hyperemia. In this patient, who died about twenty-four hours after the last injection, which was followed by the usual type of convulsion, there was considerable congestion in all sections taken from numerous regions of the brain. We believe that the petechial hemorrhages were bleeding by diapedesis due to increased permeability of the vessel walls, many of which showed swollen endothelium; fine pigment granules were commonly seen in the entire vessel wall, especially capillaries and arterioles. We believe that the process began early in the course of treatment with metrazol, as evidenced by the several areas of demyelination in the cerebral white

9. Liebert, E., and Weil, A.: Histopathologic Changes in the Brain Following Injections of Metrazol, Arch. Neurol. & Psychiat. **42**:690 (Oct.) 1939.

matter (fig. 4). These areas, which contained some blood, showed neither fat nor a glial reaction. Only an occasional thrombosed meningeal vessel was seen, and we believe that the clots were formed after the hemorrhage and were not the cause of the petechial bleedings. Although neuronophagia is present in the hippocampus bilaterally, we have been unable to find the severe destruction of the cornu ammonis described by Liebert and Weil [9] as observed in rabbit brains.

SUMMARY

A case is described of death due to subarachnoid and intracerebral hemorrhages following the ninth injection of metrazol (5 cc.). It is believed that the hemorrhages were due to increased permeability of the vessel walls caused by the toxic effects of metrazol and degeneration of the liver.

The opinion is expressed that, since therapy with metrazol appears to be less dangerous than was originally believed, its contraindications are few, and psychotic patients with some physical complications should be given the benefit of metrazol shock therapy.

DEFECTIVE CLOSURE OF THE NEURAL TUBE

A Case of Involvement of the Central Olfactory, Trigeminal Mesencephalic, Visual Reflex, Auditory and Cerebellar Systems

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In another communication dealing with cerebellar agenesis [1] it was pointed out that in addition to aplasia of the cerebellum and its related extracerebellar structures defects were observed in a number of structures which were functionally entirely unrelated to the cerebellum. This neuropathy was so extensive and the combination so unusual that it appeared advisable to report these findings as a separate study.

REPORT OF CASE

History.—The story concerning the patient (a Negro) and the method of studying the brain were included in the previous report. In brief, it was observed that in spite of marked neural defects the man adjusted well during all but the last three years of his life, when a generalized arteriosclerotic process caused a striking deterioration of personality. At the time of admission to the hospital he was disoriented, displayed poor memory and was markedly tremulous. After two and one-half years in the hospital he died at the age of 72, from pulmonary tuberculosis.

The pathologic observations related to the cerebellum and its associated pathways were previously reviewed.[1] Briefly, it may be stated that the cerebellum was markedly attenuated, being limited to a poorly developed flocculonodular lobe. The middle cerebellar peduncles were markedly hypoplastic, and the inferior olivary nuclei and their tracts were exceedingly diminutive.

Extracerebellar changes were related to the olfactory, trigeminal mesencephalic, visual reflex, auditory and vestibular mechanisms.

Olfactory System.—This showed grave defects on the right side (fig. 1). The defects were particularly noted in the hypoplasia of the fornix, in the mamillary body, in the mamillothalamic bundle on this side and possibly also in the amygdaloid nucleus. The taenia thalami were also poorly stained. The habenular ganglion and the anterior nucleus of the thalamus showed lesser degrees of disturbance but were definitely involved. The fasciculus retroflexus on the right side also appeared attenuated, but the interpeduncular nucleus was preserved. The anterior commissure stained lightly on the right side, and the hippocampus on this side also seemed to be hypoplastic.

Optic System.—This was essentially normal. The anterior hypothalamic (Gudden's) commissure, which accompanies the optic chiasm, was well demarcated,

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1. Rubinstein, H. S., and Freeman, W.: Cerebellar Agenesis, J. Nerv. & Ment. Dis., to be published.

and the lateral geniculate bodies showed a normal arrangement of cells bilaterally. Likewise, the pulvinar was normal throughout. The field of Wernicke was normal in extent and staining tendencies. The visual sensory mechanism was therefore normal.

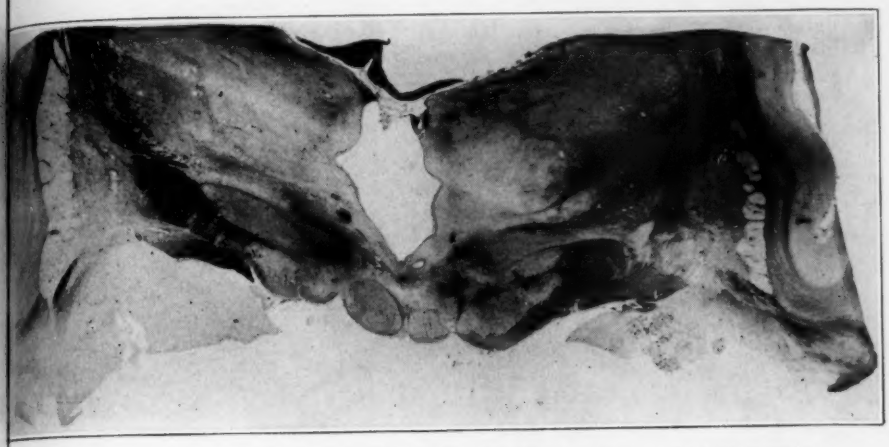

Fig. 1.—Section through the mamillary bodies, showing the marked attenuation of this structure on the right. The right fornix, the taenia thalami, the mamillothalamic tract and the retroflex tract are also involved.

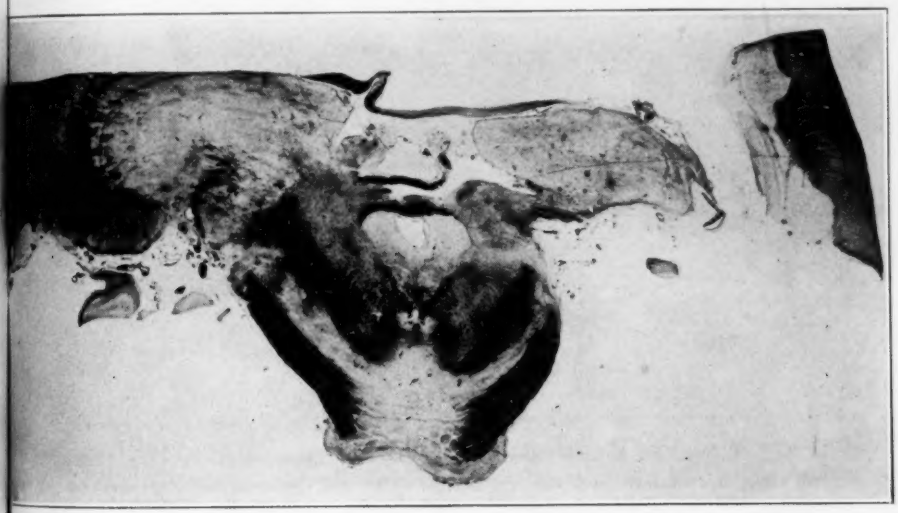

Fig. 2.—Section through the superior colliculi, showing the defects on the right. The oculomotor nerves appear equal bilaterally. The fornix on the right is absent.

Visuoreflex System.—This was apparently defective (fig. 2). The right superior colliculus seemed to have suffered from an extension of a defect which involved the neural tube just caudal to it. This superior colliculus was therefore

smaller, less regularly laminated and less distinctly demarcated from the central gray matter than was the left superior colliculus. In places, the lack in structural orientation resulted from small islands of pia, glia and chromatophore cells which were present in its interior. The commissural fibers of the superior colliculi were attenuated on the right. The posterior commissure and the medial longitudinal fasciculus, however, were intact bilaterally.

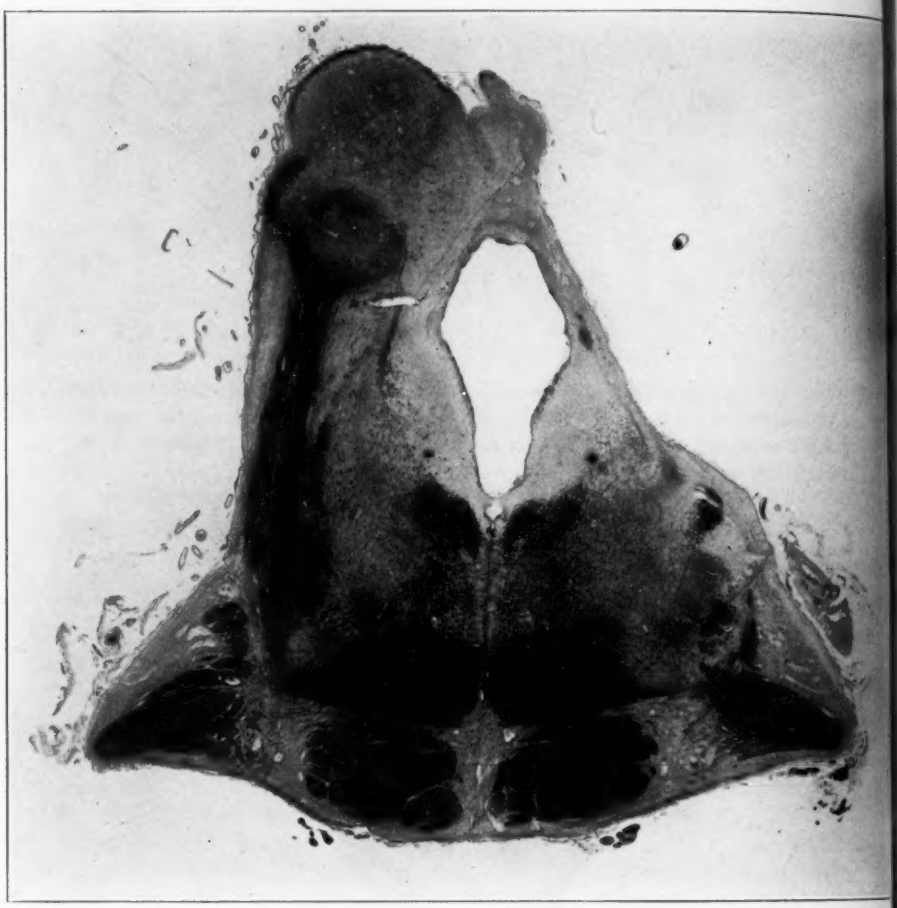

Fig. 3.—Section through the inferior colliculi, showing the striking defect in the right dorsolateral wall of the neural tube and the dilatation of the cerebral aqueduct. The lateral fillet, the nucleus of the lateral fillet and the inferior colliculus are replaced by a thin glial band through which passes the trochlear nerve. The mesencephalic trigeminal system is also defective on the right side.

Oculomotor System.—The oculomotor nuclear complex was essentially normal. The fourth nerve on the right, however, took a devious course through the glia, making up the right lateral wall of the distal aqueduct (fig. 3) and decussated in the roof of a large cavity at the level of the knee of the facial nerve. The medial

longitudinal fasciculus was of good caliber throughout and lost itself among some poorly defined collections of medium-sized cells which lay in the floor of the third ventricle (really a dilated aqueduct), somewhat lateral to the oculomotor nucleus. These cells constituted the nucleus of the posterior commissure (nucleus of Darkshevich) and the nucleus of the medial longitudinal fasciculus (nucleus interstitialis of Cajal) respectively. It was definite that some of these fibers ended on cells of the nucleus of the posterior commissure and perhaps even among the cells of the dorsal tegmental nucleus, which is closely related (in position) to the oculomotor nucleus.

Mesencephalic Nucleus of the Fifth Nerve.—Examination of sections of the midbrain revealed a marked deficiency in the trigeminal mesencephalic system on

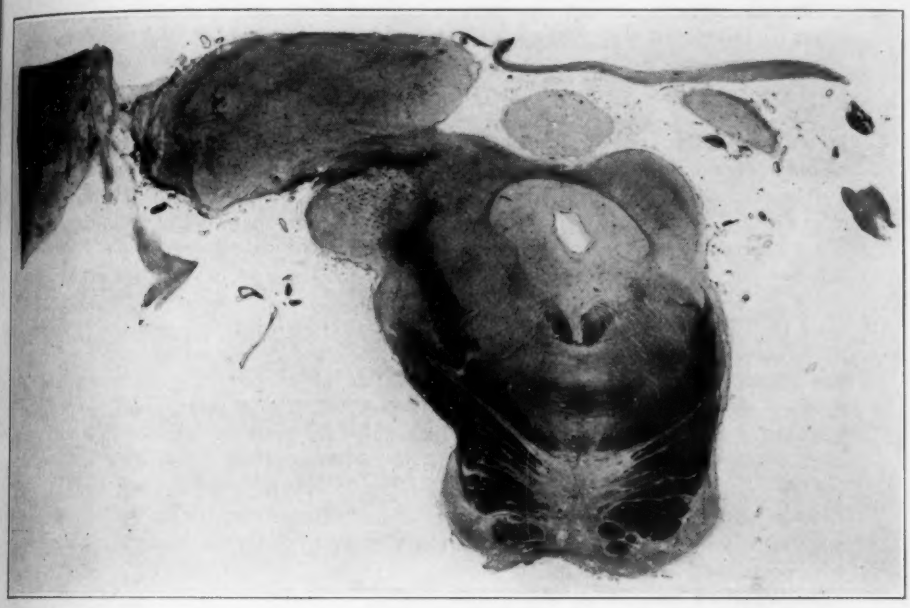

Fig. 4.—Section through the more proximal level of the inferior colliculi, showing the partial repair of the neural tube. The left lateral fillet is entering the medial geniculate body.

the right side (fig. 4). The defect was particularly striking in the area corresponding to the wedge-shaped lesion between the tegmentum and the tectum. The remnants of the system on the right could be observed, however, as low as the level of the nucleus abducens and as high as that of the oculomotor nucleus. Although the left mesencephalic trigeminal system was better developed than that of the right side, one obtained the impression that this trigeminal nucleus and tract were also attenuated.

Auditory System.—The cochlear division of the eighth nerve on entering the brain stem penetrated a well marked cochlear nucleus. While the left dorsal cochlear nucleus was large, that on the right was small, possessing relatively few cells, most of which were small. The tuberculum acusticum was moderately well marked in the region of the lateral recess of the fourth ventricle; the corpus

pontobulbare was small and inconspicuous. The auditory nerve divided on entering the brain stem to form the poorly defined striae acusticae and a well marked trapezoid body which was related to the laterally lying nuclear material, the nucleus of the trapezoid body and the superior olive. Fascicular cells were scattered all the way across the trapezoid body, which tended to run within the medial lemniscus. The weak striae acusticae of the floor of the fourth ventricle ultimately joined the lateral lemniscus on the left, while on the right they appeared to be lost, in common with the lateral fillet and the inferior colliculus of this side. The lateral fillet on the left was well defined, lying between the cerebellar white matter and the brachium conjunctivum. A fairly well defined nucleus of the lateral fillet was visible on the left side (fig. 3), but none was seen on the right. The left lateral fillet passed in part into the inferior colliculus, which was somewhat smaller than normal and had a less dense feltwork of fibers about it. Moreover, there were few, if any, crossing fibers between the two sides. Practically, there was neither a lateral fillet nor an inferior colliculus on the right side.

The remaining fibers of the left lateral lemniscus passed to the left medial geniculate body (fig. 2), which made its appearance in the most proximal section of the midbrain, at a level where the defect of the right neural tube was becoming visibly smaller. This corresponded to the level of the broadest portion of the fillet (medial and lateral) system, which soon became large and joined the appearing thalamic structure. At this level the medial geniculate body of the right side had not yet become visible. This absence of the right medial geniculate body could not be attributed solely to difference in the plane of section on the two sides, since the structure was absent also in sections clearly showing the right thalamus. Moreover, it began to appear only at a level where the defect in the neural wall had practically disappeared. The first indication of its presence was observed through the brachium of the inferior colliculus, which was seen passing to an indefinitely organized structure of the thalamus. Its presence was short lived, since it was not seen at any level proximal to its fellow of the opposite side.

The right medial geniculate body was not only smaller than the left but, in contrast with its normal-appearing fellow, contained rather numerous spots with large atheromatous vessels sometimes surrounded by more or less hyalinized areas with occassional small infarcts.

Vestibular System.—The two fasciculi making up the eighth nerves could easily be differentiated. The vestibular component situated between the more dorsally lying cochlear division and the more ventrally disposed corpus pontobulbare could be seen running dorsally to connect with a strongly developed descending nucleus and tract. It appeared smaller, however, than the corresponding system of the normal person.

The triangular medial nucleus (nucleus of Schwalbe) was well developed. The lateral nucleus (nucleus of Deiters) was made up of rather sparsely scattered cells and came into close relation with the defective dentate nucleus. The development was considerably better on the left side than on the right, although the superior and lateral nuclei showed less difference than did the medial and spinal nuclei. The medial nuclei could still be identified proximal to the level of the dentate nucleus. The fibers of the superior nucleus apparently swept down into the flocculus, the only cerebellar structure approaching adequate development. Fibers running medially from the vestibular complex could be seen as an indefinite tract engaging the abducens nucleus and possibly going to the medial longitudinal fasciculus.

The medial nucleus could be followed distally to a level corresponding to the more proximal emerging fibers of the hypoglossal nerve, while the spinal nucleus finally seemed to disappear by fusing with the medial part of the nucleus cuneatus. No well defined vestibulospinal tracts could be identified.

Somatic Afferent System (for Contact Stimuli).—The dorsal columns were prominent features in the lowermost section; the nucleus gracilis and the nucleus cuneatus were well developed. They did not, however, show inordinate development, and, although they were proportionately large, this enlargement was by no means absolute. The median fillet appeared broader and flatter than normal and was made up of very compact bands of fibers that stood out exceptionally well because of the attenuation of neighboring structures in the medulla. When actually compared with normal specimens, however, they did not appear to be absolutely larger than normal. The two medial lemnisci ultimately reached the lateral nuclei of the thalamus. The left thalamus was the seat of some small infarcts.

Spinothalamic Tract.—This fasciculus became evident in distal sections of the medulla, where it lay ventral to the substantia gelatinosa. It occupied a rather prominent position owing to the diminutive spinocerebellar system. In the proximal part of the medulla it lay between the inferior olivary nucleus and the spinal root of the trigeminal nerve, where it probably combined with fibers of the rubrospinal, the tectospinal and other tracts. It was crisscrossed by fibers passing from the inferior olive to the restiform bodies and by transverse acoustic fibers entering into the trapezoid body and the superior olive. With entry of the fifth nerve and dorsal migration of the fillet the spinothalamic tract became obscured and more or less fused with the median fillet, so that it could no longer be recognized as a distinct bundle. It probably entered the thalamus together with the medial fillet.

Corticospinal System.—The pyramidal tract was somewhat paler and less voluminous on the left side than on the right. No cortical lesion was observed to explain the difference in the size of these tracts. The internal capsule on the left side was somewhat more diffuse and definitely smaller than that on the right (fig. 5). In the peduncle the pyramidal tracts were less than half as large as normal, appearing grossly as rather thin ribbons just ventral to the substantia nigra.

In the proximal level of the pons they became more or less separated into fasciculi, and the more medially placed fibers on the left side appeared paler than the rest of the bundle. In the distal part of the pons (fig. 6) the tracts maintained themselves as distinct bundles separated by a rather prominent fissure. Their course through the pons was very short owing to the deficiency of the pontile system. On entry into the medulla they occupied a normal position and decussated in its distal part in a manner similar to that seen in normal specimens.

Corpus Striatum.—The tail and body of the caudate nucleus seemed to be normal. The putamen was of good size and, though not large, showed normal architecture and good position. A few small infarcts were seen here and there, mostly of the sclerotic and pigmented type, but no gross lesions were discernible. The globus pallidus appeared to be of average size, possessed a normal architecture and was free from lesions.

Thalamus.—The thalamus was partially described in connection with the somatic afferent system. It may be noted here that the lateral nucleus of the left side was somewhat atrophic, particularly in its lateral portion. The pulvinar and the anterior and medial nuclei were intact. The atrophy was apparently a retrograde change due to the cortical lesions (infarcts). The centre médian (Luys) and the arciform nuclei were distinguishable and appeared normal.

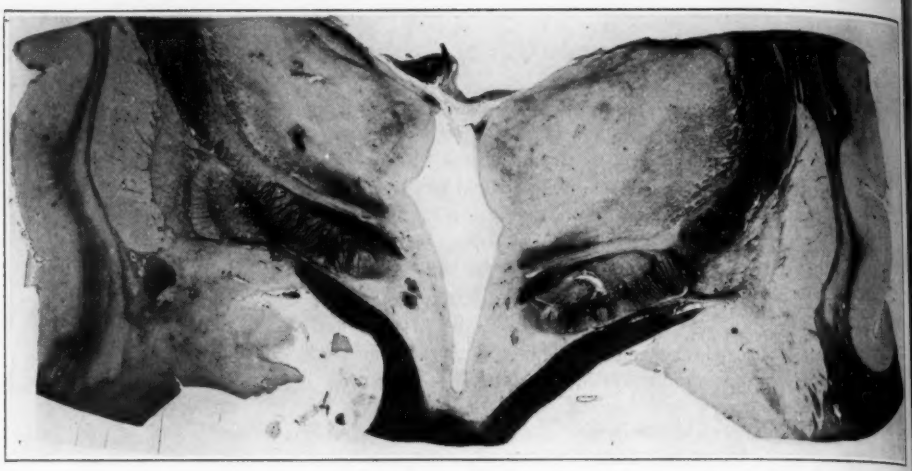

Fig. 5.—Section showing the internal capsule on the left to be smaller and more diffuse than the one on the right. On the right the fornix is seen to be lacking near its origin and over the thalamus. It is to be noted that the hypothalamic nuclear zone is well demarcated.

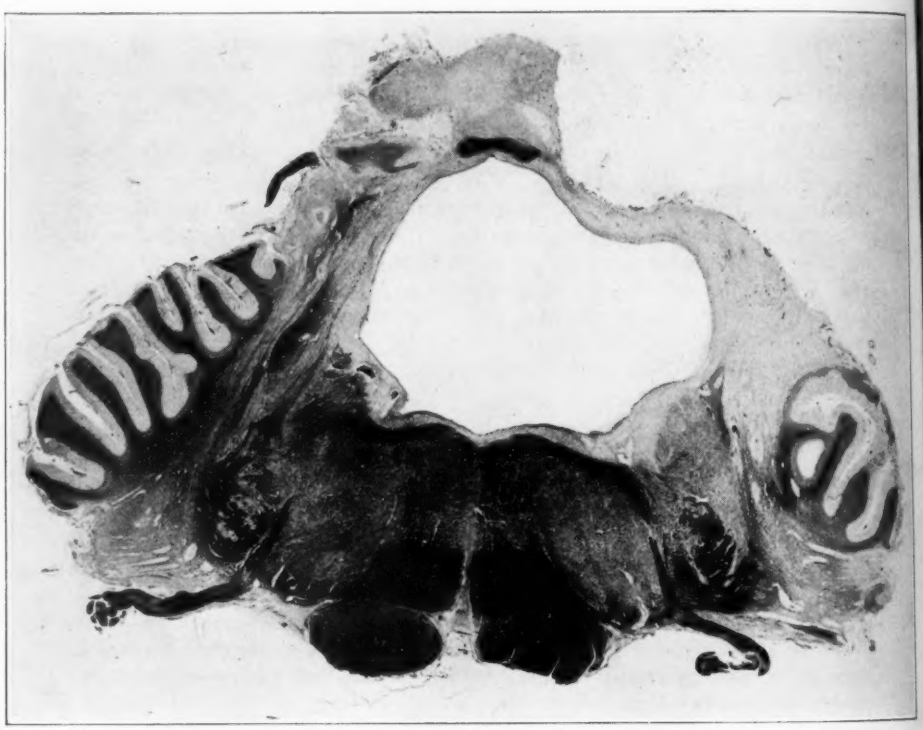

Fig. 6.—Through the genu and the emerging fibers of the facial nerve, showing the decussation of the trochlear nerves, the glial roof of the fourth ventricle uniting the flocculi, the rather small pyramids and the sparsity of pontile fibers. The vestibular complex is relatively intact.

Corpus Subthalamicum.—This body was well developed and possessed normal-appearing cells. It was well surrounded by myelinated fibers (fig. 1). The perforating fibers could distinctly be seen passing between the subthalamic body and the globus pallidus. Ventromesially these fibers hooked around the cerebral peduncle to form a well defined ansa lenticularis. More dorsolaterally, they appeared to run from the globus pallidus through the peduncular (pyramidal) tract to form the dorsal capsular wall of the nucleus subthalamicus, as the field H_2. A well marked field H_1 could be seen separated from field H_2 by the zona incerta, which lay just lateral to the mamillothalamic tract.

Substantia Nigra.—This was seen as an exceptionally large nucleus which extended dorsally into the region of the nucleus ruber and up along the raphe of the midbrain into the region of the oculomotor nucleus.

Hypothalamic Nuclei.—The nucleus tuberis, nucleus supraopticus, nucleus paraventricularis and nucleus paramedianus were recognizable as small structures, well defined in the gray matter of the floor (nucleus tuberis and nucleus supraopticus) and walls (nucleus paraventricularis, ventrally; nucleus paramedianus, dorsally) of the third ventricle. The substantia grisea centralis was not particularly well supplied with ganglion cells, but no striking abnormality was seen.

Miscellaneous Observations.—In the rather disrupted condition of the brain at the time of study it was difficult to make out all the architectural details. However, from what could be observed the olfactory tracts appeared to be equivalent on the two sides, and the olfactory trigon, although somewhat mutilated, appeared fairly normal.

The anterior commissure was seen as a large bundle and appeared grossly normal. The pillars of the fornix on the right side were much reduced in size. The corpus callosum was of fair thickness. The anterior and posterior horns of the lateral ventricle were moderately dilated.

The two hippocampi were observed to be cut free from the rest of the brain, the one on the right side being smaller than that on the left. On superficial inspection the hippocampal digitations were not well pronounced. Cross section of these structures (hippocampi) disclosed an apparently malformed architecture, particularly on the right side, so that the various layers could not be recognized.

COMMENT

While the cerebellum and its associated structures were bilaterally attenuated, the extracerebellar neuropathy remained unilateral. For this reason it is believed that the defects noted were the result of two processes: (1) a genetic defect leading to attenuation of the neocerebellar mechanism bilaterally and (2) a defective closure of the neural tube just to the right of the dorsal midline, involving the region of the diencephalon and mesencephalon.

The striking feature in this case was the ability of the patient to go through the major part of his life without detection of his marked defect. The absence of cerebellar phenomena was considered to result from a constitutional inferiority which was so generalized that the man could "get by" on the low psychosomatic level at which he functioned.[1] It would appear, however, from the extent of the extracerebellar pathologic changes that antemortem symptoms or signs should have been marked, and yet, aside from sluggish pupillary reflexes, no striking dysfunctions were observed. Of course, as he neared death the

patient became markedly disoriented, dysarthric and ataxic, but this, as has been mentioned, was attributed to the later atherosclerotic involvement of the cerebrum.

The grave defects of the olfactory system on the right side may be said to have included both afferent and efferent mechanisms. When one considers that the right olfactory tract was intact and that impulses traversing this pathway reach the rather extensive cortex of the uncus and the hippocampal gyrus by devious paths, it becomes obvious that the afferent impulses checked by the taenia thalami may reach their destination through the intact stria terminalis, the septal fibers and the medial and lateral longitudinal striae in addition to the more direct pathway passing from the anterior perforated space to the uncus. Similarly, efferent olfactory responses originating in the uncus or the hippocampus of one side could have reached the lower vegetative centers bilaterally through the hippocampal commissure (lyre of David). It is thus evident that a lesion involving only one fornix may leave the olfactory function for the most part intact. As a matter of fact, in the patient described here the interpeduncular nucleus (nucleus of Ganser) which receives impulses from both retroflex tracts (tracts of Meynert) was entirely intact.

Generally, lesions involving the central olfactory mechanism, as in cases of tumor [2] or of degenerative neuropathies, result in episodic subjective olfactory phenomena in which the patient senses nonexistent odors rather than in a loss of olfactory perception. When the peripheral portions of the rhinencephalon, however, become involved, as in the case of tumor of the frontal lobe or of direct involvement of the olfactory tract, distinct unilateral anosmia may ensue.[3]

The bilaterally small corpora pontobulbaria observed in this patient are of interest because, in spite of their position in the pons embryologically, they are believed to arise from the proximolateral walls of the lateral recess [4] in common with the flocculi. Their bilateral attenuation in association with bilateral cerebellar agenesis seems to corroborate this opinion.

The defective trigeminal mesencephalic system on one side could also exist without apparent effect. This is true particularly if the function of this tract is afferent proprioceptive from the muscles of mastication,[5] since the jaw muscles of both sides act simultaneously, and impulses from the intact side could allow for a sense of awareness of the position of the jaw.

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2. Jackson, J. H., and Beevan, C. E.: Case of Tumor of the Right Temporo-Sphenoid Lobe Bearing on the Localization of the Sense of Smell and on the Interpretation of a Particular Variety of Epilepsy, Brain **12**:346, 1890.

3. Elsberg, C. A., and Brewer, E. D.: The Sense of Smell: X. A Detailed Description of the Technique of Two Olfactory Tests Used for the Localization of Supratentorial Tumors of the Brain, Bull. Neurol. Inst. New York **4**:500, 1935.

4. Larsell, O.: The Cerebellum: A Review and Interpretation, Arch. Neurol. & Psychiat. **38**:580 (Sept.) 1937.

5. Willems, E.: Les noyaux masticateurs et mésencéphaliques du trijumeau chez le lapin, Névraxe **12**:7, 1911. Allen, W. F.: Application of Marchi Method to the Study of the Radix Mesencephalica Trigemini in the Guinea Pig, J. Comp. Neurol. **30**:169, 1919.

The marked defect of the auditory system existing without apparent discomfort to the patient is again analogous to the condition found in the olfactory mechanism. However, while in man the olfactory system plays a relatively minor role so far as the total personality is concerned,[6] the function of hearing in man is extremely important. The damage to the auditory tract noted in this patient included damage to the right lateral lemniscus and the inferior colliculus. As in the case of the olfactory system, auditory impulses entering the neuraxis from either side ascend the brain stem bilaterally, so that as long as any primary receptory nucleus is intact it is possible for impulses of that side to reach the cerebrum. It is conceivable that in this patient auditory impulses traversing the right auditory nerve could enter the intact right dorsal cochlear nucleus and by means of the intact trapezoid body pass to the lateral lemniscus of the opposite side. The patient could therefore hear sufficiently to "get along" at his level of existence without awareness of his auditory deficiency. Unfortunately, since the neuropathy remained unsuspected during the patient's life, refined audiometry was not considered.

The defective vestibular mechanism was considered in another communication,[1] but here again it was thought that sufficient equipment remained which, together with the diminutive cerebellum, could supply all the synergic and equilibratory control that this man required for his crude motor purposes.

The presence of bilaterally sluggish pupillary light reflexes in the presence of rather marked hypoplasia of the right superior colliculus is interesting. On the basis of earlier reports[7] which postulated the flow of constrictopupillary impulses from the optic tract to the superior colliculus, one was led to believe that damage to one superior colliculus would abolish the light reflex or at least lead to unilateral pupillary changes. Later observations on cats and monkeys[8] have shown that afferent light impulses destined for pupillary constriction traverse the optic tracts along the medial margin of the lateral geniculate body to enter the brachium of the superior colliculus, through which they are transmitted to the neuraxis.

The neuraxial level in which they terminate is not the superior colliculus but the thalamomesencephalic junction (pretectal area). After synapse in the pretectal area, secondary fibers take two courses. (1) through the posterior commissure to end in the Edinger-Westphal nucleus of the contralateral side and (2) distoventromedially to ter-

6. Fulton, J. F.: Physiology of the Nervous System, New York, Oxford University Press, 1938.

7. Harris, W.: The Fibers of the Pupillary Reflex and the Argyll Robertson Pupil, Arch. Neurol. & Psychiat. **34**:1195 (Dec.) 1935.

8. (*a*) Ranson, S. W., and Magoun, H. W.: The Central Path of the Pupillo-constrictor Reflex in Response to Light, Arch. Neurol. & Psychiat. **30**:1193 (Dec.) 1933. (*b*) Hare, W. K.; Magoun, H. W., and Ranson, S. W.: Pathways for Pupillary Constriction: Location of Synapses in the Path for Pupillary Light Reflex and Constrictor Fibers of Cortical Origins ibid. **34**:1188 (Dec.) 1935. (*c*) Barris, R. W.: A Pupillo-Constrictor Area in the Cerebral Cortex of the Cat and Its Relation to the Pretectal Area, J. Comp. Neurol. **63**:353, 1936.

minate in the Edinger-Westphal nucleus of the ipsilateral side. That all fibers destined for the contralateral Edinger-Westphal nucleus do not cross through the posterior commissure may be gathered from the fact that midline section of the posterior commissure reduces but does not abolish the consensual light reflex. While this observation was made on the cat,[8a,b] it probably also holds for higher mammals, since in apes the crossing fibers in the posterior commissure are probably less numerous than in the cat.[6]

It is obvious from this that a defect in the neural tube which involves one superior colliculus and even the posterior commissure can still spare the light reflex. In this case the lesion did not extend to the pretectal region, nor did it involve the medial border of the lateral geniculate body. Some of the commissural fibers must have been involved, however, since the pupillary light reflexes were sluggish bilaterally.

SUMMARY AND CONCLUSION

The extracerebellar defects which were observed in a case of bilateral cerebellar agenesis have been described. The patient, a Negro aged 72, in spite of his marked neuropathy, went through the major portion of his life (sixty-nine years) without detection of his defect. The extracerebellar aberrations were unilateral and involved the olfactory, the trigeminal mesencephalic, the visual reflex, the auditory and the vestibular mechanism. These were believed to be due to defective closure of the neural tube. In spite of the extensive structural aberrations the patient failed to attract attention during the major part of his life, and the defects, which included bilateral cerebellar agenesis, were discovered only at autopsy. The defects have been analyzed anatomically and physiologically, and it is concluded that for the most part associated neural tracts were sufficient to convey enough impulses through the defective neural tube to allow this man to live at his relatively low psychosomatic level with the condition unnoticed.

Aid in the preparation of this study was given by the neuropathologic laboratory of the Henry Phipps Psychiatric Clinic, through the cooperation of Dr. Adolf Meyer.

DEATH OF DR. SINGER

As the final form for this issue was going to press, word was received of the untimely death of the Chief Editor, Dr. H. Douglas Singer, in New Mexico, on August 28, following a heat stroke. An obituary will appear in a later issue.

News and Comment

THE AMERICAN COLLEGE OF PHYSICIANS

The twenty-fifth annual session of the American College of Physicians will be held in Boston, with general headquarters at the Statler Hotel, April 21 to 25, 1941. Dr. James D. Bruce, of Ann Arbor, Mich., is president of the college and will have charge of the program of general scientific sessions. Dr. William B. Breed, of Boston, has been appointed general chairman of the session, and will be in charge of the program of clinics and demonstrations in the hospitals and medical schools and of the program of panel and round table discussions to be conducted at the headquarters.

MASSACHUSETTS SOCIETY FOR RESEARCH IN PSYCHIATRY

On May 2, 1940 the Massachusetts Society for Research in Psychiatry was officially organized and held its first meeting. The object of the society is to stimulate research in psychiatric medicine and the sciences allied to it.

The membership includes active and associate members, active membership being limited to those who have completed, read before a recognized scientific society or published in a recognized scientific journal the results of research work done within the last five years. Active membership will cease after more than three years have elapsed without production of original work, the member becoming an associate member. Associate members are selected from those having a satisfactory background and training to render them suitably qualified to become research workers, and from those who are participating in research work. Meetings will be held six times a year at the various hospitals in Massachusetts engaged in neuropsychiatric work. They will be devoted to symposiums, and also to informal discussions of projects, methods, technics and demonstrations of research work actively engaged in or under discussion.

The following officers were elected: president, William Malamud, M.D.; vice president, Paul Yakovlev, M.D., and secretary-treasurer, Kenneth J. Tillotson.

QUARTERLY JOURNAL OF STUDIES ON ALCOHOL

A new quarterly journal, dealing with studies on alcohol, has just been initiated, the first number appearing in June 1940. As the British journal *Inebriety* has now been discontinued, this periodical, the *Quarterly Journal of Studies on Alcohol,* is the only one in the English language devoted solely to the problems of alcohol. It is published by the Journal of Studies on Alcohol, Inc., 4 Hillhouse Avenue, New Haven, Conn.

The annual subscription price is $3 and a single issue $1. The journal is edited by a board consisting of the following: Emil Bogen, Karl M. Bowman, Anton J. Carlson, Thorne M. Carpenter, Hans T. Clarke, Harry R. DeSilva, Alexander O. Gettler, Leon A. Greenberg, Howard W. Haggard, Rolla N. Harger, Yandell Henderson, Norman Jolliffe, William de B. MacNider, Merrill Moore, Abraham Myerson, Winfred Overholser, Nathan Rakieten, Eugene V. Rostow, Thorsten Sellin, Edward A. Strecker and Ray Lyman Wilbur.

SOUTHERN PSYCHIATRIC ASSOCIATION

The Southern Psychiatric Association will hold its annual convention at Jacksonville, Fla., on Oct. 21 and 22, 1940.

Abstracts from Current Literature

Anatomy and Embryology

MELANIN PIGMENT IN THE CENTRAL NERVOUS SYSTEM OF VERTEBRATES. ALEXANDRA ADLER, J. Comp. Neurol. **70**:315 (April) 1939.

Specimens were taken from the brain and spinal cord of amphibia, fish and man and studied in unstained sections and after staining with methylene blue (methylthionine chloride U. S. P.) and neutral red. When pigment was observed, special staining procedures were applied to determine its nature. No melanin was seen in the nerve cells of two species of Caecilians, the lowest form studied. In a specimen of Necturus 60 mm. long, melanin granules were present, whereas in specimens 31 and 95 mm. in length none were seen. In a 5 inch (12.7 cm.) specimen of Proteus anguineus, about one in eight ganglion cells contained melanin. Other species of amphibia which undergo metamorphosis showed small amounts of melanin. Melanin was not seen in the nerve cells of fish.

Human brains taken shortly after birth and at the ages of 1, 4, 18, 20, 30, 50 and 68 years, respectively, were examined. In the brain of the newborn and in that of the child aged 1 melanin was absent. In the brain of the child aged 4 fine granules were present. In the brains of persons from 18 to 50 years of age the amount of pigment was constant, while in the brains of the 2 subjects aged 68 the amount was much more abundant. The melanin pigment was observed in three centers, the locus caeruleus, the dorsal nucleus of the vagus and the substantia nigra.

FRASER, Philadelphia.

THE CEREBRAL CORTEX OF RHEA AMERICANA. E. HORNE CRAIGIE, J. Comp. Neurol. **70**:331 (June) 1939.

Craigie studied the cerebral cortex of 5 specimens of Rhea americana, one of the most primitive living orders of birds, which is placed between the ostriches, on the one hand, and the cassowaries and emus, on the other. The brains were prepared with cresyl violet, Davenport's silver technic and Weil's myelin stain. Craigie compares the brain of Rhea with that of the ostrich, the emu, the chick, the loon and the hummingbird. The fiber connections are in general similar to those in other birds. The cortex resembles that of other ratite birds.

ADDISON, Philadelphia.

NOTES ON THE COMPARATIVE ANATOMY OF THE SENSORY AREAS OF THE VERTEBRATE INNER EAR. JEAN K. WESTON, J. Comp. Neurol. **70**:355 (June) 1939.

Weston measured the approximate extent of the sensory areas of the inner ear of 24 species of verebrates, from Petromyzon to man. The right and the left ear were found to have a sensory area of about the same size. The smallest total sensory area of the inner ear in any adult form was observed in Proteus anguineus. The variations in size of the area in different species suggested a correlation with physiologic activity. The crista externa was usually somewhat smaller, relatively, than the average for the two vertical cristae. The macula sacculi had a greater range of size than the macula lagenae. The size of the papilla basilaris varied from very small in amphibians and some reptiles to very large in man.

ADDISON, Philadelphia.

STUDIES ON THE SIZE OF THE CELLS IN THE CEREBRAL CORTEX: III. THE STRIATE AREA OF MAN, ORANG AND CEBUS. GERHARDT VON BONIN, J. Comp. Neurol. **70**:395 (June) 1939.

Von Bonin attempted to discover how far the size of cells depends on their localization at various depths of the cortex in man, orang and Cebus. For this study he used Brodmann's area 17, the area striata. Conspicuously large cells were present in layers IVB and V. Fibers from the optic radiation ended around the perikaryon of such cells in layer IVB. The cells in this layer were stellate, whereas the cells in layer V were pyramidal. The average nuclear volume was greatest in man, less in the orang and least in Cebus. The giant stellate cells showed practically the same nuclear volume in all three species. The size of the solitary large pyramidal cells was greatest in man and least in Cebus, but their relative size was about the same in all three forms. The curves for size and depth showed differences between the species. Von Bonin suggests that the curves show evolutionary changes unsuspected by methods of study previously used.

ADDISON, Philadelphia.

NEURONOPHAGIA IN THE BRAIN OF THE MOUSE AS A RESULT OF INANITION, AND IN THE NORMAL AGING PROCESS. WARREN ANDREW, J. Comp. Neurol. **70**:413 (June) 1939.

Andrew studied the changes in nerve cells resulting from inanition in mice of various ages, from youth to old age. Two animals each were killed at the ages of 45, 79 and 163 days, and 1 animal each at the ages of 691, 702 and 739 days. The left halves of the brains were prepared for demonstration of the Golgi apparatus, and the right halves, for demonstration of the Nissl substances. All stages of neuronophagia were seen in the cerebral cortex of the starved mice. The pyramidal cells appeared as in brains of senile mice. The cells were shrunken and irregular. The earliest stages of the process of neuronophagia showed the glia nucleus in close contact with the pyramidal cell body, usually at the base. The action of the glia cell appeared to be first cytolytic rather than phagocytic. The nucleus of the nerve cell was very resistant to the action of the glia cells and was often seen with only a narrow crescent of cytoplasm remaining. The nucleus apparently was finally ingested. The substance of an entire nerve cell might be ingested by a single glia cell, or five or six glia cells might take part in the process. Neuronophagia was observed in normal, senile mice, but it was a much slower process than in starving animals.

FRASER, Philadelphia.

THE ORIGIN AND DEVELOPMENT OF TASTE ORGANS IN SALAMANDERS OBSERVED IN THE LIVING CONDITION. L. S. STONE, J. Exper. Zoöl. **83**:481 (April) 1940.

Experiments were carried out on 113 embryos and larvae of Amblystoma punctatum. Most observations were made under high magnification on living specimens placed in microaquariums. Grafts of the tongue anlage of embryos or of the tip of the tongue of larvae were transferred from donors to the side of the body or the tail fin of recipients of the same age. Specimens ranging from early tail-bud stages to larvae 33 mm. in length were used. It was found that taste buds develop on the side of the body in grafts removed from presumptive tongue tissue long before the gustatory nerves have begun to develop. Normal taste organs also developed when the tongue anlage was transplanted just before, during or after the period when taste organs normally appear, at a time when the gustatory nerves reach the tongue. The sense organs and the graft persisted until after metamorphosis, when new skin invaded the transplant. Stone concludes that gustatory nerves have nothing to do with the origin of taste organs in Amblystoma, and that they do not play a prominent part as a nutrient factor in maintaining the taste organs. It was also shown that new organs are produced by a budding process from the peripheral cells of other organs.

WYMAN, Boston.

PROJECTION OF THE ANTERIOR NUCLEI OF THE THALAMUS TO THE INTERHEMISPHERIC CORTEX. J. STOFFELS, J. belge de neurol. et de psychiat. **39**:743 (Nov.); 783 (Dec.) 1939.

Stoffels comes to the following conclusions, based on a detailed study of the connections of the anterior thalamic nuclei in the rabbit: The anteromedian, internal parataenial and paramedian nuclei and the anterior portion of the median nucleus have projection fibers to the anterior portion of the interhemispheric cortex; the anteroventral nucleus has projections to the posterior and middle portions, and the lateral nucleus has projections in part to the area peristriata. Stoffels found the anteroventral nucleus to be related to the area retrosplenialis granularis, dorsalis and ventralis, and the area infraradiata posterior; the anteromedian nucleus to the area infraradiata anterior, dorsalis and intermedia; the paramedian nucleus to the area infraradiata anterior ventralis; the internal parataenial nucleus to the area retrobulbaris and the taenia tecta; the anterior portion of the median nucleus to the area frontopolaris and the anterodorsal nucleus to the area praesubicularis. There is a systematic anteroposterior localization in the cortex corresponding to the nuclei connected with the various areas.

DE JONG, Ann Arbor, Mich.

SPECIAL INNERVATION OF THE STRIATED MUSCLE FIBERS OF THE ESOPHAGUS. KEN KURÉ, S. OKINAKA, T. SAKURAI and D. KONDO, Arch. f. d. ges. Physiol. **243**:403, 1939.

After cutting the vagus nerve at various levels in young dogs, the authors studied the subsequent degeneration in the medulla oblongata and in the peripheral nerve. They were particularly interested in the relationship of Jacobson's nucleus pigmentosus nervi vagi to the vagus. This nucleus lies at the level of the lower pole of the inferior olive, ventromedial to the reticular formation. Its fibers run first in the vagal ramus of the accessory nerve, then in the trunk of the vagus nerve. They consist of thin myelinated fibers and end chiefly in the esophagus. After severance of the roots of the vagus nerve the fibers degenerate to the peripheral endings in the esophagus. Destruction of the esophageal branches causes retrograde degeneration of the cells of the nucleus pigmentosus. Nicotine poisoning showed that these fibers run, without interruption in a ganglion, directly to the striated muscle fibers in the esophagus. On stimulation of these fibers the esophagus promptly contracts like a voluntary muscle. The endings of these fibers are paralyzed by curare but not by atropine.

SPIEGEL, Philadelphia.

Physiology and Biochemistry

EFFECT OF REPEATED INSULIN HYPOGLYCEMIA ON THE LIPID COMPOSITION OF RABBIT TISSUES. L. O. RANDALL, J. Biol. Chem. **133**:129, 1940.

Repeated hypoglycemic convulsions were induced with insulin in 17 rabbits. Seventeen untreated rabbits served as controls. The brain, liver, kidney, spleen, muscle and adrenal glands were analyzed for lipids. The insulin treatment produced a small but statistically significant decrease in the phosphatide and neutral fat contents of nerve tissue, but no change in the amount of cholesterol. The amounts of phosphatide and cholesterol were not significantly affected in the liver, kidney, spleen and muscle. Neutral fat was increased significantly in the liver and kidney only. The adrenal glands were hypertrophied. In these glands the absolute amounts of phosphatide and neutral fat were increased, while free and ester cholesterol remained constant. The percentages of phosphatide and free cholesterol remained constant, that of ester cholesterol was decreased and that of neutral fat was increased.

PAGE, Indianapolis.

EFFECT OF TESTOSTERONE ON SERUM LIPIDS IN SCHIZOPHRENIA. L. O. RANDALL, J. Biol. Chem. **133**:137, 1940.

The injection of testosterone propionate, during a period of three weeks, in 9 schizophrenic subjects produced a continuous rise in serum lipids followed by a return toward the initial level after medication. Injections of sesame oil had no significant effect in 10 subjects. The present results indicate that testosterone may play a part in the maintenance of normal lipid metabolism.

PAGE, Indianapolis.

MELANIN PIGMENTATION OF THE SUBSTANTIA NIGRA IN PRIMATES. H. J. SCHERER, J. Comp. Neurol. **71**:91 (Aug.) 1939.

Scherer studied the melanin pigmentation of the substantia nigra, locus caeruleus and pia mater in 3 chimpanzees, orang-utans, 2 gibbons, 3 lemurs and various Cercopithecidae. Sections were prepared to show Nissl substance or pigmentation by the Masson method of silver impregnation. Melanin was observed to some extent in the brains of all the primates studied. The pigment in the substantia nigra of the chimpanzee and of 1 orang-utan was dark gray; it was reddish in all but 2 of the lower primates. The pigment was more abundant and darker in the older animals, as far as their ages could be ascertained. Melanin was also seen in the locus caeruleus and in the pia. The pigmentation in the locus caeruleus was less intense than in man, while that in the pia was more intense.

FRASER, Philadelphia.

AUTONOMIC RESPONSES TO ELECTRICAL STIMULATION OF THE LOWER BRAIN STEM. S. C. WANG and S. W. RANSON, J. Comp. Neurol. **71**:437 (Dec.) 1939.

Wang and Ranson stimulated the medulla and pons of cats by means of the stereotaxic instrument. Blood pressure and bladder tension were recorded, and any change in size of the pupil was noted. In the pontile region mild vasomotor responses were elicited, and the areas were scattered in the tegmentum and the periventricular gray substance. At the levels of the superior olive and the facial nucleus areas for pressor responses were located largely in the lateral reticular formation. Reactive points were scattered also in the region corresponding to the facial nucleus and the superior olivary nucleus. Stimulation of the medulla at the rostral end of the inferior olive, and more caudally, yielded much more frequent large pressor reactions, although the general distribution of the pressor and depressor areas in the reticular formation remained the same as at the preceding levels. From the ventral portion of the lateral reticular formation there were obtained nine depressor and three pressor responses. In the floor of the fourth ventricle is the so-called pressor area, or myelencephalic sympathetic center, which corresponds in general location to the medial vestibular nucleus and the dorsal motor nucleus of the vagus nerve. Contractions of the urinary bladder were obtained by stimulation of the ventromedial border of the inferior colliculus and the brachium conjunctivum. Positive responses of the bladder were obtained from stimulation in the ventral portion of the lateral reticular formation and the superior olivary nucleus. Slight dilatation of the pupil was obtained from almost any point in the lower portion of the brain stem when stimulated with a weak current. Points giving maximal bilateral pupillary dilatation were more or less confined to the tegmental region of the pons and the lateral reticular formation of the medulla.

ADDISON, Philadelphia.

DESCENDING PATHWAYS FROM THE HYPOTHALAMUS TO THE MEDULLA AND SPINAL CORD. OBSERVATIONS ON BLOOD PRESSURE AND BLADDER RESPONSES. S. C. WANG and S. W. RANSON, J. Comp. Neurol. **71**:457 (Dec.) 1939.

Wang and Ranson stimulated the hypothalamus of 45 cats by use of the stereotaxic instrument and recorded changes in blood pressure and bladder tension. The medulla or the spinal cord was sectioned and stimulation of the same region was repeated. After completion of each experiment the appropriate segment of the medulla or spinal cord was prepared by a myelin technic. In the medulla the hypothalamic efferent pressor pathway occupied a large area in the lateral reticular formation. The descending pathway mediating bladder responses descended in a more restricted area of the same region. Both pressor and bladder impulses descended in the ventrolateral column of the spinal cord, with partial decussation in the brain stem.

ADDISON, Philadelphia.

FURTHER EXPERIMENTS ON THE RELATIONS BETWEEN OPTIC STIMULI AND THE INCREASE OR DECREASE OF PIGMENT IN FISHES. FRANCIS B. SUMNER, J. Exper. Zoöl. **83**:327 (March) 1940.

Specimens of the guppy, Lebistes reticulatus, were exposed for two months to backgrounds of five shades (black, white and gray), under uniform overhead illumination. In another experiment the fish were exposed for six weeks to four grades of illumination. The effect of these conditions on the production or loss of melanophores was determined by counting the pigment cells in a given area of skin. The response to the background was such that the number of melanophores tended to vary inversely as the logarithm of its albedo. The intensity of incident light had little, if any, effect on the number of melanophores. The amount of xanthophyll accumulated by the fish also varied with the albedo, being much greater in those from the darker backgrounds.

WYMAN, Boston.

HYPOGLYCAEMIC SHOCK AND THE GRASP-REFLEX. A. KENNEDY, J. Neurol. & Psychiat. **3**:27 (Jan.) 1940.

Kennedy induced hypoglycemic shock in 6 Macacus rhesus monkeys and observed that the phenomena were essentially similar to those seen in man during therapeutic hypoglycemia. In the monkey the grasp reflex, as determined by the hanging response, constantly appeared during the precoma stage, from eighty to one hundred minutes after injection of the insulin, disappeared from one hundred and sixty to one hundred and seventy minutes after the injection, when the coma deepened, and reappeared briefly during the phase of recovery. The hypoglycemic shock was not associated with cataleptic phenomena. Injections of bulbocapnine alone produced the characteristic phenomena of akinesis, tremor, salivation and mild catalepsy and the immediate appearance of a grasp reflex. Injection of bulbocapnine during various phases of the hypoglycemic shock produced general effects and a hanging response which could be considered as a summation of the individual effects of the two drugs. However, when bulbocapnine was injected after the hanging response produced by hypoglycemia had already appeared, new phenomena occurred, namely, disappearance of the usual tremors produced by bulbocapnine and the appearance of spontaneous grasping and a grasp reflex obtainable on light stimulation of the palm. It was found that insulin had no effect on the catalepsy induced by bulbocapnine. From these observations, Kennedy concludes that the action of insulin is depressant, predominantly on the cerebral cortex, since the neuromuscular excitability, drowsiness and akinesia characterizing the hypoglycemic shock and the appearance of a grasp reflex can be regarded as release phenomena.

MALAMUD, Ann Arbor, Mich.

Neuropathology

PATHOLOGIC FACTORS FOUND IN SURGICAL INVESTIGATION OF EPILEPSY. K. W. NEY, Am. J. Surg. **47**:573 (March) 1940.

In a series of 272 patients with the "idiopathic" type of epilepsy, Ney almost invariably observed definite lesions at operation. In 225 cases corticodural fixations at the cerebral vertex in or near the cortical motor areas were localized roentgenologically with the aid of subdural insufflation of air. Arachnoid defects or fistulas through which cerebrospinal fluid leaks into the subdural space were found in practically every epileptic patient on whom operation was performed. These fistulas are probably the result of tears in the arachnoid which have failed to heal. They are usually located at the extreme vertex of the brain, where the strain of gravity is greatest. During subdural air insufflation it is possible to demonstrate that cerebral postural stability is dependent on the maintenance of arachnoid-dural approximation. This approximation is controlled by fluid film adhesion between the arachnoid and the dura, which maintains these structures in forceful apposition, and a negative subdural pressure, which develops when fluid film adhesion is lost through an excess of subdural fluid. This subdural negative pressure maintains the brain in a certain degree of postural stability, but tends to siphon cerebrospinal fluid into the subdural space through arachnoid fistulas when these are present. The traction on the cortex which occurs with expansive lesions and corticodural adhesions after craniocerebral trauma seems to be a factor responsible for the induction of convulsive phenomena in these two diverse pathologic conditions. During operation, traction serves to induce attacks. In the "idiopathic" type of epilepsy definite traction is exerted on corticodural attachments at the extreme vertex of the brain during postural displacement, which occurs when there is an excess of subdural fluid. Subdural air insufflation aids in the localization of corticodural attachments. It shows the cerebral postural displacement which takes place when air or excessive fluid enters the subdural space. The fluid level changes with the position of the head. The surgical correction of arachnoid fistulas and the reduction of traction on corticodural attachments have so diminished convulsive attacks in his cases that the author feels justified in considering the lesions described as causative factors in chronic convulsive states.

J. A. M. A.

MYASTHENIA GRAVIS AND THE THYMUS GLAND. H. G. MILLER, Arch. Path. **29**:212 (Feb.) 1940.

Miller discusses the association of tumor of the thymus gland and myasthenia gravis, first described by Weigert in 1901. Weigert called the thymic lesion a lymphosarcoma and looked on the lymphorrhages in the voluntary muscles as metastases. This viewpoint has been disproved by numerous authors. Miller reviews 5 cases of myasthenia gravis encountered among 16,300 autopsies at the Johns Hopkins Hospital. In 2 cases encapsulated tumors of the thymus gland were found, with remnants of normal thymus outside the capsule; in 2 the thymus gland was persistent, with well marked peripheral epithelial hyperplasia in 1 instance, and in 1 case the thymus was not identified. This investigation brings the total number of cases in which a lesion of the thymus was discovered to 41, in a series of 87 cases of myasthenia gravis studied.

Miller suggests that patients with myasthenia gravis be subjected to careful roentgen examination and that irradiation and surgical removal be employed more frequently because of the unfavorable progress under even the newer methods of therapy.

WINKELMAN, Philadelphia.

SYMMETRIC NECROSIS OF THE GLOBUS PALLIDUS IN BARBITURATE POISONING. A. DEGROAT, Arch. Path. **29**:271 (Feb.) 1940.

A nurse aged 24 was found unconscious from what was interpreted as an overdose of barbiturates. She died five days later of bronchopneumonia. At autopsy there were observed edema of the brain, symmetric softening of the globus pallidus, bronchopneumonia and fatty degeneration of the liver. The author interprets the changes in the brain as the result of prolonged deep asphyxia followed by survival for several days. He does not believe that the barbiturates exert a specific effect on the globus pallidus.

WINKELMAN, Philadelphia.

SIMMONDS' DISEASE (PITUITARY CACHEXIA) IN AN AGED MAN WITH DEMENTIA PRAECOX. MYRTELLE M. CANAVAN, Arch. Path. **29**:310 (March) 1940.

Canavan reports the case of a man aged 72 who died three months after a fracture of the femur. There had been loss of weight of about 45 pounds (20.4 Kg.) despite sufficient food intake. At autopsy the stomach was observed to be no larger than the gallbladder, the testes were atrophic and the pituitary gland was very small. Microscopically, the anterior lobe of the pituitary body consisted chiefly of collapsed and dull polychromatic, edematous cells and showed many free nuclei and shadows of cell outlines. The acidophil showed vacuolation of cytoplasm; the basophils were few but the chromophobes appeared normal.

WINKELMAN, Philadelphia.

MALIGNANT ADENOMAS OF THE CHROMOPHOBE CELLS OF THE PITUITARY BODY. ORVILLE T. BAILEY and ELLIOTT C. CUTLER, Arch. Path. **29**:368 (March) 1940.

Bailey and Cutler report 3 cases of malignant tumors arising from the chromophobe cells of the pars anterior of the pituitary body. These differed clinically from the usual case of benign chromophobe adenoma in the history of rapid progression of symptoms and in the rapid extension of the tumor into the skull bones adjacent to the sella turcica, the neighboring brain substance and the nasopharynx. The early stages of the illness were dominated in the first case by ocular symptoms, in the second by uncinate seizures and in the third by nasal obstruction.

Histologically, the tumors were characterized by arrangement of the tumor cells in broad sheets separated from one another by a stroma which was altered in character from that of the normal pars anterior and was in part derived from structures at the edge of the tumor, far from the sella turcica.

Such tumors are set apart from the usual chromophobe adenomas and designated in a distinctive way. The term "malignant chromophobe adenoma" indicates that they are locally invasive and possess certain of the histologic characteristics of malignant tumors but do not metastasize in the cerebrospinal axis or elsewhere in the body. The malignant chromophobe adenoma presents certain difficulties in differential diagnosis, especially in distinguishing it from chordoma and carcinoma of the sphenoid sinus or of the nasopharynx. The tendency of the malignant chromophobe adenoma to include large blood vessels in the sellar region makes surgical approach to it especially perilous. One of the 3 patients showed a satisfactory response to roentgen therapy, including the control of symptoms pointing to involvement of the temporal lobe. The other 2 patients, who were treated surgically, died.

WINKELMAN, Philadelphia.

NEURONOPHAGIA IN THE HUMAN CEREBRAL CORTEX IN SENILITY AND IN PATHOLOGIC CONDITIONS. WARREN ANDREW and EDWARD SINTON CARDWELL JR., Arch. Path. **29**:400 (March) 1940.

Neuronophagia, a process of lysis and ingestion of nerve cells, as demonstrated in the mouse, occurs in the human cerebral cortex in senility and in a variety of pathologic conditions. This process is most active in the layer of polymorphic cells. There is an increase in the degree of satellitosis about the large pyramidal cells with advancing age. Loss of Nissl material and increase in the basophilic properties of the nuclei are found in most older persons and are believed to be natural phenomena of ageing in man.

WINKELMAN, Philadelphia.

NOTES ON THE PATHOGENESIS AND MORPHOLOGY OF NEW-GROWTHS, MALFORMATIONS AND DEFORMITIES OF THE INTRACRANIAL BLOOD-VESSELS. N. G. EVANS and C. B. COURVILLE, Bull. Los Angeles Neurol. Soc. **4**:145 (Dec.) 1939.

Evans and Courville report 102 cases of gross lesions of the intracranial blood vessels and propose a classification based on developmental and morphologic characteristics. They divide all such lesions into four groups. 1. True tumors were found in 12 cases in the series, in 10 of which the lesion was angioblastic meningioma and in 2 cerebellar hemangioblastoma. Tumors of the latter type occur in the cerebellum, medulla and spinal cord, tend to be multiple and correspond to the hemangioendotheliomas seen elsewhere in the body. They are often associated with other congenital vascular anomalies, especially in the liver and kidneys. Angioblastic meningioma may, in the authors' opinion, be the supratentorial representative of hemangioblastoma.

2. Congenital vascular malformations were represented by 22 cases. Of these, 2 were anomalies of the dural sinuses, 18 anomalies of the veins of the brain (such as varices and venous angiomas of plexiform, small cavernous or large racemose type) and 2 anomalies of both arteries and veins (racemose arteriovenous angiomas). A fourth type of vascular anomaly was not represented, viz., purely arterial malformations, including arterial varices and racemose arterial angiomas. Evans and Courville believe that the development of the various angiomatous malformations is due to perversion of the normal morphogenesis of the cerebral blood vessels, as outlined in five stages by Streeter.

3. Aneurysmal dilatation of arteries was present in 68 cases in the series. These included 62 instances of saccular aneurysm, large and small, considered to be due to congenital weakness in the medial coat at points of bifurcation, and 6 cases of fusiform aneurysm, thought to be of arteriosclerotic origin. The saccular arterial aneurysm was thus by far the most common lesion observed. When small this aneurysm is symptomless until it ruptures, but when large it may produce neighborhood signs by local pressure, or even signs of elevated intracranial tension.

4. Carotid-cavernous sinus (arteriovenous) aneurysms were not encountered in the series. This type, however, characterized by pulsating exophthalmos, is the only true, acquired, intracranial arteriovenous aneurysm, and is perhaps the most common form of arteriovenous fistula found in the body.

MACKAY, Chicago.

DEGENERATION OF THE PAPILLO-MACULAR BUNDLE IN APES AND ITS SIGNIFICANCE IN HUMAN NEUROPATHOLOGY. H. J. SCHERER, J. Neurol. & Psychiat. **3**:37 (Jan.) 1940.

In 8 of 27 monkeys in which the optic pathways were studied histologically, Scherer found spontaneous system degeneration of the papillomacular bundle without other demonstrable changes in the nervous system. The lesions were identical in all cases and showed a symmetric fascicular distribution restricted to the fibers

of the papillomacular bundle and characterized histologically by initial deposition of fat in fixed glia elements, which later progressed to distinct demyelination. The lesions differed only in the degree and extent of degeneration of the optic pathways, apparently beginning in the tracts and later involving the optic nerves. Similar changes in the optic pathways were observed by Scherer in apes with subacute combined degeneration of the spinal or central type. The spontaneous lesions frequently occurred during the terminal stage of systemic diseases. This fact and the frequent association with subacute combined degeneration suggested that degeneration of the papillomacular bundle may be caused by nutritional deficiency, analogous to similar etiologic factors in retrobulbar neuritis and subacute combined degeneration in man.

MALAMUD, Ann Arbor, Mich.

ANATOMIC AND PATHOGENIC STUDY OF METASTATIC CEREBRAL TUMORS. H. ROGER, L. CORNIL and J. E. PAILLAS, Rev. neurol. **72**:137, 1939.

Of 28 cases of metastatic tumors of the brain, the neoplasm was epithelial in 21, sarcomatous in 5 and melanomatous in 2 cases. Over one third of the primary tumors were carcinomas of the lung. Many other primary sites were associated with metastases to the lung, so that in half of all the cases there were either primary or metastatic tumors of the lung. Carcinoma of the breast was second in frequency, with an incidence of 20 per cent. In most cases the cerebral metastases were bilateral and were distributed along the course of the main cerebral arteries. They were often bilateral and symmetric. Metastases were more frequent in the parenchyma than in the meninges or the cranial nerves. Metastases in the choroid plexus were rare. The meningeal nodules were firm, while those within the brain were soft and, when large, necrotic and often liquid in the center. In some cases air or thorium dioxide was injected into a liquefied tumor during the ventriculographic procedure. Intracerebral tumors have no connective tissue stroma and are poorly vascularized. They extend into the surrounding tissue along the Virchow-Robin spaces and compress the arteries. The neighboring tissue presents edema, malacia and hemorrhage, often at a distance from the tumor, sometimes in the opposite hemisphere. The spinal cord in some cases showed vacuolation of the columns and degeneration of the gray matter and edema, which explains the absence of tendon reflexes observed. The tumor may reach the brain by three routes: (1) arterial, followed by tumors of the lung; (2) lymphatic, followed by tumors of the breast and leading to meningeal metastases, and (3) neural, followed by tumors of the breast and tumors of the face and cavum.

LIBER, New York.

ANATOMICOCLINICAL STUDY OF A STRIOCEREBELLAR SYNDROME WITH BRADYKINESIS AND CHOLESTEROSIS OF THE SPLEEN AND CHOROID PLEXUS. C. DE MORSIER and L. VAN BOGAERT, Confinia neurol. **2**:321, 1939.

De Morsier and van Bogaert report the case of a woman aged 64 who had a progressive extrapyramidal syndrome starting at the age of 8 and developing over the course of 50 years in the form of a striocerebellar tremor, with bradykinesis, myoclonias, involuntary movements of the face and dysarthria. There were some psychic changes. Pathologic examination revealed symmetric status fibrosus in the putamen and the caudate nucleus on each side, with demyelination and gliosis in the external segment of the globus pallidus. There were also gliosis in the white matter of the cerebrum and cerebellum and in the superior cerebellar peduncles and rarefaction of the Purkinje cells. The red nucleus and the substantia nigra were not involved. In addition, there was cholesterosis of the choroid plexus and spleen. The authors believe that the splenochoroid component in this case was related to visceral and neural cholesterosis, but state that the cerebral parenchyma was free from such deposits.

DE JONG, Ann Arbor, Mich.

Psychiatry and Psychopathology

THE SIGNIFICANCE OF SPECIAL MENTAL TESTS FOR DIAGNOSIS AND PROGNOSIS IN SCHIZOPHRENIA. K. GOLDSTEIN, Am. J. Psychiat. **96**:575, 1939.

Instead of studying isolated symptoms, such as changes in thinking and language, Goldstein emphasizes the changes in the total personality and the experimental approach. He draws a distinction between abstract and concrete types of human behavior. The abstract is conceptual or categorical; the concrete is realistic. In addition, abstract behavior is more active. Goldstein emphasizes that gradations exist between the two extremes in normal persons, and that a person can shift from one to the other as the need arises. Organic disease of the brain tends to reduce a person to the concrete level. In the determinations, sorting tests were used. The impairment of abstract attitude found in schizophrenic patients by these tests is similar to that found in persons with organic disease, so that organic involvement is predicated as the primary cause. Somatic therapy may be promising in removing this change toward the concrete attitude, and thus bringing the patient again to a position in which psychotherapy is available. In the future these tests may offer aid in prognosis, as well as in determining the nature of psychotherapy to be administered.

FORSTER, Boston.

PSYCHOSES ASSOCIATED WITH EPILEPSY. R. J. CLARK and J. M. LESKO, Am. J. Psychiat. **96**:595, 1939.

Clark and Lesko studied 22 patients with psychosis associated with idiopathic epilepsy. Fourteen of these had clouded states, 3 chronic psychoses, 1 deterioration with psychosis, 1 a severe behavior disorder and 3 unclassified conditions. The ages varied from 12 to 49; seizures had been present for an average of fifteen years. All patients had grand mal epilepsy, with an average frequency of one attack a month. The 14 patients with clouded states showed an average duration of the psychosis of four and a half days for twenty-one episodes. These were usually preceded by grand mal attacks. All patients in this group were overactive at some time during the psychosis; 12 had delusions.

An unclassified condition is described in a boy aged 16; he presented psychomotor equivalents as well as temper tantrums, with resentment toward his father and no evidence of clouding. In 3 cases of the chronic type the psychosis resembled schizophrenia.

Clark and Lesko point out that deprivation of oxygen can play only a small role in the causation of the psychosis, and they compare the clouded states with pathologic intoxication from alcohol. The possibility that the clouded state is a release phenomenon is pointed out, and these states are compared with temporary schizophrenic attacks. The authors believe that the chronic psychoses arise from the same disorder as does the epilepsy.

FORSTER, Boston.

PSYCHIATRIC ASPECTS OF PORENCEPHALY. E. L. BERNSTEIN, Am. J. Psychiat. **96**:723, 1939.

Bernstein describes 7 cases of porencephaly among approximately 1,000 patients in a psychiatric clinic. Heredity was poor in 5 cases. Inability to adjust socially was the most striking feature, followed by mental retardation. The patients were sluggish, plodding, dependent, inadequate, seclusive, resentful and defensive. They were superficial and irritable, and variations in mood were outstanding. Bernstein believes that the psychiatric picture did not differ greatly from that usually seen in epileptic patients. When the lesion was in the frontal lobes, as occurred in 2 cases, the patients were more definitely antisocial.

FORSTER, Boston.

A Psychiatric Survey of Bronchial Asthma. N. T. McDermott and S. Cobb, Psychosom. Med. **1**:203 (April) 1939.

In a detailed review of the literature, McDermott and Cobb discovered that in recent years bronchial asthma had been considered chiefly from the allergic standpoint. A study of the psychogenic factors had been made by relatively few workers, and the relative importance of the emotional life in the production of asthma had been a subject of dispute. The authors studied 50 cases of bronchial asthma in the allergy clinic of a large hospital. Thirty of the patients gave a history of emotional factors in relation to the asthma; in 7 the existence of emotional factors was discovered. The study was made on the basis of data obtained by means of a single two hour interview. In the group with evidence of emotional factors there was predominance of females, in a ratio of about 2:1, in the group not exhibiting emotional factors males predominated by a similar ratio. The antecedent family history disclosed evidence of nervous disease in 47 per cent of the "emotional" group, while such evidence was obtained in only 15 per cent of the "nonemotional" group. A trend toward a higher incidence of asthma in the first-born was noted in this series. Neurotic traits were shown by two thirds of the "emotional" and by one third of the "nonemotional" group. As compared with a control group, it was found that a considerably larger percentage of asthmatic patients had compulsive neurotic manifestations, such as exaggerated orderliness and cleanliness. The first attacks of asthma seemed to have been clearly precipitated by emotional factors in 10 cases, while in 10 others such precipitation of the attack seemed questionable. Later asthmatic attacks appeared to have been precipitated by psychic factors in 31 cases, but in only 21 of these was the evidence convincing. In 2 cases the asthmatic attacks were abruptly terminated by a strong emotion, but in both instances mild annoyances were capable of precipitating or aggravating the attacks. On the basis of the patients' own opinions regarding the value of somatic treatment, it was found that only 20 per cent of the "emotional" group were benefited, while 54 per cent of the "nonemotional" group were helped.

Schlezinger, Philadelphia.

The Correlations Between Ovarian Activity and Psychodynamic Processes. T. Benedek and B. B. Rubenstein, Psychosom. Med. **1**:245 (April) 1939.

By means of a coordinated investigation in which 75 menstrual cycles of 9 patients were carefully observed during the course of psychoanalysis, Benedek and Rubenstein have correlated the emotional and hormonal states. They made their physiologic and psychologic observations independently. The physiologic study consisted of an evaluation of the gonad function by means of the "vaginal smear-basal body temperature technique," while the psychologic investigation consisted of interpretation of psychologic material, obtained chiefly from dreams, associations and transference. In this article the findings obtained during the ovulative phase of menstruation are considered. The preovulative period is characterized by active heterosexual tendencies, which appear normally as a wish for sexual gratification but may be transformed into aggression or into a fearful defensive attitude. The ovulative period is characterized by sudden relaxation of the preovulative tension and by a beginning narcissistic erotization of the body. The latter increases during the postovulative period, resulting in a passive-receptive and narcissistic attitude. Estrone (theelin, ketohydroxyestrin) activity is conspicuous in the preovulative phase, while progestin (corpus luteum hormone) activity is correlated with the postovulative phase. The authors conclude that their study offers laboratory results supporting the theoretic concepts of psychoanalysis with regard to instincts. Their method allows a closer scrutiny of the biologic basis of instincts.

Schlezinger, Philadelphia.

AFFECTIVE STATES AND SKIN TEMPERATURE. B. MITTELMANN and H. G. WOLFF, Psychosom. Med. **1**:271 (April) 1939.

Mittelmann and Wolff studied the variations in temperature of the skin of the extremities which occurred under emotional tension produced experimentally. The results were recorded under standardized conditions by means of a Hardy radiometer. Control periods were obtained by means of rest and relaxation. The usual method of inducing an emotional state consisted of discussion of difficulties in the subject's life situation. In almost all instances emotional changes were associated with a decrease in the skin temperature, although the extent of the fall in different persons varied greatly. Major changes in temperature as a result of emotional stress were observed to occur both with and without awareness. The fall in temperature appeared to be greater during a period of sustained apprehension than during periods of sustained contentment. Patients with Raynaud's syndrome showed changes in temperature similar to those of other subjects, but the marked drops in temperature resulting from emotional stress were constantly accompanied by pain and cyanosis. Major alterations in skin temperature did not occur in patients under emotional strain if the sympathetic innervation to the extremities had been interrupted.

SCHLEZINGER, Philadelphia.

THE EMOTIONAL AND SOMATIC RESPONSE OF SCHIZOPHRENIC PATIENTS AND NORMAL CONTROLS TO ADRENALIN AND DORYL. J. B. DYNES and H. TOD, J. Neurol. & Psychiat. **3**:1 (Jan.) 1940.

Dynes and Tod investigated the emotional reactions and the peripheral autonomic responses to intramuscular injection of epinephrine and doryl (carbaminoylcholine chloride) in 10 patients with chronic schizophrenia showing clinical evidence of emotional deterioration. The results were compared with the reactions in a normal control group. The authors found that the somatic response to both drugs, as determined by their effects on the blood sugar, pulse rate, blood pressure, peristalsis, urgency of elimination, sweating, pallor, flushing, salivation and lacrimation, was adequate in the schizophrenic group. The response was in fact frequently more intense, although exhibiting a greater variability and wider range than in the normal group. This indicated that the adaptive mechanisms of the schizophrenic patient to preserve the "steady state" are defective under stress. On the other hand, the emotional response to epinephrine, such as anxiety or fear reactions, was entirely lacking in the schizophrenic patients, as compared with its marked effect in the normal group. The injection of doryl produced no affective response in either group. Such a reaction to epinephrine indicates a disorder of the emotional mechanism at a physiologic level in schizophrenia. Although the authors are cautious in their interpretation, they assert that this might be attributed to a disturbance in the central autonomic connections, for example, in the hypothalamus.

MALAMUD, Ann Arbor, Mich.

Diseases of the Brain

ADIE'S SYNDROME. JOHN MCDOWELL MCKINNEY and MAURICE FROCHT, Am. J. M. Sc. **199**:546 (April) 1940.

McKinney and Frocht state that the typical tonic pupil most frequently is fixed to light, dilates slightly in the dark and reacts tonically in accommodation. The tonic reaction is characterized by a slow response to the stimulus, usually with a latent period or delay before the response begins to take place. The differential diagnosis of Adie's syndrome includes the Argyll Robertson pupil, diphtheria, epidemic encephalitis, myotonia congenita and anisocoria. The etiologic agent remains unknown, but it is suggested that a peculiarly selective lesion in the pretectal region may account for all of the phenomena. Adie's syndrome is a disease sui generis, running a chronic and benign course and may exist alone or in conjunction with other diseases. It is perhaps heredodegenerative, but it is not syphilitic.

MICHAELS, Boston.

THE BIOCHEMISTRY OF EPILEPSY. H. GOLDSTEIN and R. A. MCFARLAND, Am. J. Psychiat. **96**:771, 1940.

Goldstein and McFarland, in a comprehensive review of the literature, found few clearcut and definite biochemical abnormalities associated with epilepsy. They gain the impression rather, that the abnormality consists of a greater variability in the constituents. As a result of the seizure there are an increase in sugar and calcium in the blood and, depending on the severity of the attack, a decrease in the p_H. These findings, however, are not statistically reliable. There is no conclusive evidence that seizures are related to abnormalities of dextrose tolerance. The hour to hour variation and the daily range of the p_H appear to be greater in epileptic than in normal persons. As a result of the seizure there is slight temporary acidosis. Studies of blood gases have not revealed generalized cerebral anoxemia, nor is induction of this state a certain method of producing seizures. No correlation has been found between calcium values and epileptic seizures, but the blood calcium values for epileptic persons show a wider range than normal. Studies of protein metabolism have been negative for the most part. An increase of fibrinogen in the blood is the only chemical abnormality found in epileptic subjects. Nitrogen retention seems to be an effect rather than a cause of the seizure. Low cholesterol values with wide variability are reported, but correlation between this and seizures is not definite.

FORSTER, Boston.

THE UNSOLVED PROBLEMS IN APHASIA: II. ALEXIA RESULTING FROM A TEMPORAL LESION. J. M. NIELSEN, Bull. Los Angeles Neurol. Soc. **4**:168 (Dec.) 1939.

From a study of 13 cases selected from the neurologic literature and 3 cases observed personally, Nielsen concludes that lesions involving the posterior portion of the major (left) superior temporal convolution, leaving the angular gyrus intact, destroy or seriously reduce comprehension of the significance of words which the patient can recognize by sight. Nielsen's attention was directed particularly to that part of the superior temporal convolution lying between Wernicke's center for comprehension of spoken words and the angular gyrus, which mediates the recognition of printed words. This area is not yet anatomically recognizable by cytoarchitectural or myelogenetic studies. However, lesions confined to the angular gyrus destroy recognition of the printed word while leaving comprehension of the spoken word intact; this demonstrates that (1) comprehension of the spoken word does not depend on its visual recognition, (2) the major (left) angular gyrus mediates recognition of the printed word and (3) the posterior limit of the area in question for comprehension of the printed word is the angular gyrus. On the other hand, with a few exceptions, lesions of the major (left) superior temporal convolution with preservation of the angular gyrus destroy comprehension of the printed as well as of the spoken word. Thus Henschen's postulate that comprehension of the spoken word is necessary for comprehension of the written word is usually true.

From these facts it is concluded that deletion of the recently acquired function of recognition of written symbols does not interfere with the already thoroughly established comprehension of spoken language; that the area concerned with the comprehension of the visual word extends from Wernicke's center into the angular gyrus, and that such comprehension of the written word is dependent on association of the angular gyrus with Wernicke's area, while comprehension of the spoken word is not dependent on such association.

MACKAY, Chicago.

EPILEPSY AMONG COLLEGE STUDENTS. L. E. HIMLER and T. RAPHAEL, Journal-Lancet **60**:125 (March) 1940.

During a period of nine years, in which the total enrolment was 118,532, 70 students came to the attention of Himler and Raphael because of petit or grand mal seizures. Particular effort was made to exclude all cases of simple

syncope, hysterical reactions or other unconscious states not possessing the characteristics of epileptic attacks. Of the 70 epileptic students (50 men and 20 women) 44 had attacks before coming to the university and 26 had their first seizures subsequent to entrance. Grand mal attacks, with or without accompanying petit mal seizures, occurred in 64 cases and petit mal or narcoleptic attacks alone in 6 cases. The incidence (0.06 per cent) as determined for the student body is not directly comparable to the general incidence of epilepsy, but represents less than one eighth of that (0.5 per cent) estimated by Lennox for the adult population at large. Forty-six of the students came to the attention of university health service physicians after the first attack on the campus had occurred, 18 came for examination and treatment on their own initiative, and only 6 were referred by parents, friends, relatives or home physicians. Increased understanding and cooperation on the part of home physician are much to be desired and should aid greatly in the optimal procedure, not only with regard to admission but, if admission is advisable, with reference to proper planning of the curriculum and treatment during the college period. If the convulsive state were viewed and appraised by colleges and universities on its clinical merits, broadly conceived, and not as of necessity constituting a bar to positive college performance, it would do much to encourage a fuller and more frank cooperation by students, relatives and physicians.

J. A. M. A.

RELATIVES OF INSTITUTIONALIZED EPILEPTIC PERSONS. K. VOLLAND, Ztschr. f. d. ges. Neurol. u. Psychiat. **166**:735 (Oct.) 1939.

Volland studied the relatives of 300 patients with idiopathic epilepsy. All the patients were married and had children. There were 162 men and 138 women. In 72 patients the onset of the epilepsy had occurred after the age of 30. Almost all the patients had a severe form of the disease, with marked mental changes, including disorders of intellect and of affect. Sixty-five of the patients had epileptic relatives. Some had a definite familial history of epilepsy. There was no evidence for a so-called psychopathic predisposition to epilepsy. Epilepsy was the most common neuropsychiatric disorder encountered in the relatives of epileptic patients. There were 1,065 children, 18 of whom had epilepsy. The percentage of epileptic children between the ages of 5 and 30 was 1.9. The incidence of mental deficiency among the children was 2.4 per cent, of psychoses 0.8 per cent and of other mental abnormalities 3.9 per cent. The low figures in this series, as compared with others in the literature, may be explained partly by the fact that in at least 131 cases no information was obtained about the families of patients. In many cases in this series information could be obtained only by questionnaire. This method of gathering data is definitely inferior to and not as reliable as interviewing the relatives and examining them personally. It is also important to emphasize that the percentage of abnormal persons among the relatives of a given group of patients will decrease as the more restless and unstable disappear and are not available for study.

SAVITSKY, New York.

HEREDITY OF STURGE-WEBER DISEASE. GERHARD KOCH, Ztschr. f. d. ges. Neurol. u. Psychiat. **168**:614 (Feb.) 1940.

Sturge, in 1879, and Weber, in 1926, described a disease entity characterized by nevus of the face, glaucoma and cerebral symptoms, associated with intracranial calcification. Koch reports the case of a man aged 38, an imbecile, with a facial nevus, glaucoma involving the left eye and angiomatosis calcificans cerebri. He had convulsions and right hemiplegia. Two members of his family had nevi, 3 had epilepsy and 5 migraine; 4 died in early life with convulsions. The fact that the patient's mother and grandmother had migraine suggests a dominant mode of transmission. Epilepsy appeared in the collateral lines, as it usually does in the symptomatic form. The question of the existence of a sex-linked factor needs further study.

SAVITSKY, New York.

TRAUMATIC PARKINSONISM. WALTER SCHULTE, Ztschr. f. d. ges. Neurol. u. Psychiat. **168**:669 (Feb.) 1940.

Schulte believes that the disease in his case meets all the criteria for true traumatic parkinsonism. A man aged 40 was observed during November 1938 with a typical parkinsonian syndrome, which was especially marked on the left side of the body. There were a pill-rolling tremor on the left, masking of the face and changes in tonus and defective associated movements in both upper limbs. There was weakness of the left lower portion of the face.

Toward the end of 1919, when the patient was 21, he had been shot through the head during a street brawl. He was unconscious for six hours. The bullet entered the head in the right frontal region, 3.5 cm. above the right eyebrow and 1.5 cm. from the midline. The exit of the bullet was through the occipital bone, 6 inches (15 cm.) lateral to the midline, at the site of insertion of the neck muscles into the occipital bone. He was free from symptoms for five years, except for occasional dizziness. Then the left hand began to tremble. Two years later he noted stiffness and unsteadiness of the left lower limb. These changes remained limited to the left side for about ten years.

There was no family history of paralysis agitans and no history of encephalitis or influenza during periods of epidemics. The age of onset was also against the diagnosis of idiopathic parkinsonism (in 40 cases of paralysis agitans studied by the author the age of onset was 54.2 years). Study of the course of the bullet indicates that it probably passed through the right basal ganglia. The long interval between the trauma and the onset of parkinsonism does not rule out the etiologic role of the injury. Late sequelae of trauma to the head, especially epilepsy, are well known and are usually due to the slow development of scar tissue.

There are no anatomically verified cases of this type in the literature.

SAVITSKY, New York.

Diseases of the Spinal Cord

RECURRING ENCEPHALOMENINGORADICULITIS WITH FIBROMYOSITIS FOLLOWING POLIOMYELITIS: A BACTERIOLOGIC STUDY OF SIXTY-FOUR CASES. EDWARD C. ROSENOW, Arch. Int. Med. **64**:1197 (Dec.) 1939.

Rosenow studied a group of 64 patients with recurring infection, occurring in most instances during the poliomyelitis epidemics of 1934, 1935 and 1936. By employing special methods of culture, he isolated the same type of the streptococcus from the nasopharynx, the uterine cervix and the feces. During exacerbations of the disease the same type of the organism was consistently recovered from the catheterized urine, blood, spinal fluid, excised pieces of muscle and ovaries. Infiltration of the dura, especially in the lumbar region, was common, and because of the complete absence of cells in the spinal fluid of animals given injections of the streptococci Rosenow believes that the streptococci isolated from the spinal fluid were really from the infiltrated dura.

The chief symptoms and lesions in patients were reproduced experimentally by intracerebral and intravenous injections in and by feeding the streptococci to animals. The lesions in the ovaries are said to have been previously reported by others. It is believed that the deep-seated muscular pains, weakness and fatigability in the patients resulted from myositis, fibrositis, radiculitis and pachymengitis. The headaches were interpreted as due to toxicity, and not to meningeal involvement. Abdominal pain, which occurred during menstruation, was attributed to sclerosing infection of the ovaries. Rosenow states that the filtrable virus could not be demonstrated in the nasopharyngeal washings and other suspected material because of immunity to and disappearance of the virus after frank and

abortive attacks of poliomyelitis in both human beings and monkeys. It is concluded further that immunity in chronic streptococcic infections is short and that this explains the recurring remissions and exacerbations.

Rosenow concludes: (1) that the disease under study was not poliomyelitis but rather encephalomeningoradiculitis of a type usually associated with fibrositis, (2) that is was caused by a type of the streptococcus having simultaneous affinity for the nervous system, connective tissue, muscles and ovaries and (3) that this streptococcus was related to the one isolated by him during the epidemic of 1934.

BECK, Buffalo.

COMBINED DEGENERATION OF THE SPINAL CORD IN PERNICIOUS ANEMIA: RESULTS OF SEVEN YEARS' EXPERIENCE WITH PARENTAL LIVER THERAPY. M. B. STRAUSS, P. SOLOMON and H. J. FOX, New England J. Med. **222**:373 (March 7) 1940.

Strauss and his associates reported in *The Journal of the American Medical Association*, May 4, 1935, on the efficacy of parenteral liver therapy for the neural manifestations of pernicious anemia. Lesions of the spinal cord in uncomplicated pernicious anemia could be completely arrested by adequate parenterally administered liver extract. In patients without neural lesions degeneration of the spinal cord did not develop when adequate treatment was given. These conclusions were based on a study of 26 patients with marked lesions of the spinal cord and 80 patients with minimal or no neural lesions, treated for an average period of three years. Twenty-one of the first group and 64 of the second were observed for an additional four years, making a total of 85 patients observed for an average period of seven years. In none of the 21 patients with marked involvement of the spinal cord did any objective neurologic sign become more marked during the seven year period of treatment or an abnormal sign, not previously present, appear. This indicates complete arrest of the degenerative process. The 64 patients had either no signs referable to the nervous system or mild lesions not interfering with their ability to walk. In none of these has any further evidence of neural damage appeared. This indicates that adequate therapy prevents the development of degeneration of the spinal cord in pernicious anemia. Adequate treatment demands that enough extract must be given to maintain the blood values at normal. Not only should the red cells number 4,500,000 or higher, but the mean corpuscular volume should be below 100 cubic microns and the color index 1 or below. There must be no glossitis or indigestion. Recurrence of numbness, tingling or other paresthesia of the extremities calls for increase in the dose of liver extract. If the patient presents other subjective manifestations that might be attributed to progression of the lesions of the spinal cord, the dose should be doubled.

J. A. M. A.

TWO CASES OF TUMOR OF THE SPINAL CORD AT THE FORAMEN MAGNUM. M. H. WEINBERG, Confinia neurol. **2**:292, 1939.

Tumors at the foramen magnum still offer considerable difficulty in diagnosis as compared with tumors in other regions of the spinal cord. As many of these tumors are removable, especially when the diagnosis is made before much damage is done to vital areas of the cord, it is desirable to establish criteria for early diagnosis. Weinberg reports 2 cases of tumor in this region and states that a more or less definite syndrome can be established. The most characteristic finding is pain in the neck and occipital region, which is aggravated by coughing and straining and which may radiate down the arms, to the head or to between the shoulders. The evolution of other symptoms seems to depend on the extent of the tumor and the direction of its growth. When the tumor projects into the posterior fossa symptoms of increased intracranial pressure occur and papilledema may be present. There may be cerebellar signs, such as nystagmus, vertigo, ataxia and

past pointing. Astereognosis and involvement of cranial nerves may also occur. Other findings, which are observed less frequently, are increased protein content of the spinal fluid, partial or complete spinal block, atrophy of the muscles of the upper extremities and speech difficulties. DE JONG, Ann Arbor, Mich.

Treatment, Neurosurgery

USE OF METRAZOL IN THE TREATMENT OF ACUTE ALCOHOLISM. L. L. ORENSTEIN, K. BOWMAN, J. R. KAGAN and W. GOLDFARB, Am. J. Psychiat. **96**:589, 1939.

Orenstein, Bowman, Kagan and Goldfarb, for purposes of treatment, separate patients with acute alcoholism into excited and comatose groups. They studied 12,582 alcoholic patients, of whom 1,301 were psychotic, and report on the use of subconvulsive doses of metrazol in 50 patients with recent alcoholism. Thirty-four of these belong in the excited group and 16 in the comatose group. Seventy per cent of the 50 patients were improved; 22 per cent were not improved, and 8 per cent showed questionable improvement. Four cases, demonstrating the rapid improvement in each group following administration of metrazol, are reported in detail. As no change in the alcohol levels of the blood was demonstrable, the authors conclude that the results were due to the direct effects of the drug on the central nervous system. FORSTER, Boston.

NITROGEN INHALATION THERAPY FOR SCHIZOPHRENIA. F. A. D. ALEXANDER and H. E. HIMWICH, Am. J. Psychiat. **96**:643, 1939.

Alexander and Himwich offer a method of producing anoxemia by nitrogen inhalation which would remove the objections to insulin and metrazol therapy and produce a lower oxygen saturation. The apparatus is that of gaseous inhalation anesthesia. Treatments were administered three times a week. The method consists in filling the anesthesia bag with oxygen and then introducing nitrogen alone into the mask at a rate of 6 liters per minute, until the treatment is terminated by again administering oxygen. The neuromuscular changes induced are twitching of the face, followed by clonic movements of the extremities and torsion extensor spasms. The respiratory changes are the most constant and consist of increase in rate, followed by increase in volume and then arrhythmia. After termination there is apnea. Circulatory changes consist of a progressive increase in pulse rate and usually in systolic blood pressure. Electrocardiographic tracings during the treatment show the changes characteristic of anoxia. In addition to these changes, there are dilatation of the pupil, with loss of light reflex, cyanosis, salivation and sometimes incontinence. Technical considerations include adequate soda lime to remove the carbon dioxide, maintenance of sufficient gas in the bag, a close-fitting mask and comfort on the part of the patient.

Alexander and Himwich believe that the short, acute anoxia produced is unlikely to produce irreversible cerebral lesions, and they stress that the patients must be in good physical condition. They administered over 500 treatments, and found that of 13 patients who had received 300 treatments, 4 showed full remission, 1 of whom had a relapse and 8 improved. The 1 patient who did not improve had a manic-depressive psychosis with schizoid tendencies. All others had schizophrenia. FORSTER, Boston.

THE RESULTS OF SHOCK THERAPY IN THE TREATMENT OF AFFECTIVE DISORDERS. D. C. WILSON, Am. J. Psychiat. **96**:673, 1939.

Wilson advises the judicious combination of metrazol and occupational therapy, hydrotherapy and psychotherapy in the treatment of patients with affective disorders. He reports the cases of 37 patients, 19 of whom had involutional melancholia, who were treated by this method. Of the entire group, Wilson found improvement in 89 per cent, 46 per cent being greatly improved at the time of

discharge. After a follow-up study of at least five months, he found 76 per cent still improved, and of these 41 per cent were greatly improved. Of the 17 patients with involutional melancholia, Wilson found 48 per cent greatly improved and 85 per cent showing some improvement on discharge. After the follow-up 71 per cent were greatly improved.

FORSTER, Boston.

A COMPARATIVE STUDY OF HYPOGLYCEMIC SHOCK TREATMENT AND CONTROL OBSERVATION IN SCHIZOPHRENIA. J. NOTKIN, C. E. NILES, F. J. DENATALE and G. WITTMAN, Am. J. Psychiat. **96**:681, 1939.

Notkin, Niles, DeNatale and Wittman report on the follow-up study for from eight months to two years of 100 patients treated with insulin, 69 control patients and 15 patients with spontaneous improvement. Of the first group, 36 per cent showed some improvement, and of this number 47 per cent had a relapse. Of the 69 control patients, 21.7 per cent showed improvement, and of these 33.3 per cent had a relapse. When the authors added the number showing spontaneous improvement to the control group they obtained a percentage of 35.7 who showed improvement, 24 per cent of whom had a relapse. In both the treated and the control patients it was found that the highest percentage of improvement occurred in the group with the shortest duration of illness; this group also had remissions of the longest duration. Relapses occurred in 47 per cent of the treated patients and in 33.3 per cent of the control patients.

FORSTER, Boston.

THE EFFECT OF TREATMENT OF DEPRESSION IN THE MENOPAUSE WITH ESTROGENIC HORMONE. HERBERT S. RIPLEY, EPHRAIM SHORR and GEORGE PAPANICOLAOU, Am. J. Psychiat. **96**:905, 1940.

Ripley, Shorr and Papanicolaou studied 20 patients hospitalized because of menopausal or postmenopausal depressions. Six had the manic-depressive type of depression, 7 involutional melancholia and 7 reactive depressions. The ages ranged from 39 to 58, and in all cases the vaginal smear before treatment was of menopausal type. The patients received from 48,000 to 851,000 rat units of estrogen over a period of from ten to seventy days. In the group with involutional melancholia, 3 patients showed slight improvement; 4 showed none. Five of the patients with manic-depressive psychosis showed slight to moderate improvement; the other was unimproved. In the group with reactive depressions, 1 showed marked, 4 moderate and 2 slight improvement. The authors conclude that better results are obtained in treatment of milder depressions than of those which are well defined, such as involutional melancholia, and that in the group with the milder illness the endocrine therapy relieved the menopausal symptoms, so contributing to the patient's feeling of well-being and paving the way for psychotherapy.

FORSTER, Boston.

AN OBSERVATION ON THE TREATMENT OF MENTAL CASES WITH SUB-SHOCK DOSES OF INSULIN. C. R. BENNETT and T. K. MILLER, Am. J. Psychiat. **96**:961, 1940.

Bennett and Miller advocate the use of sub-shock doses of insulin in treatment of patients who offer behavior difficulties tending to make hospitalization difficult, such as overactivity, quarrelsomeness and requirement of tube feedings. Over a period of fifteen months they treated 125 patients by administering an average dose of 25 units of insulin two hours before breakfast and lunch, respectively. Under this regimen the authors found that acute manic excitements were controlled within thirty-six hours, the use of sedatives was reduced 60 per cent, the number of tube feedings was eliminated by 90 per cent, improvement in physical and mental status occurred and there was little need for a "disturbed ward."

FORSTER, Boston.

TREATMENT OF MULTIPLE SCLEROSIS WITH NICOTINIC ACID AND VITAMIN B_1. MATTHEW T. MOORE, Arch. Int. Med. **65**:1 (Jan.) 1940.

Moore was impressed by reports of flushing of the skin when nicotinic acid was used in treatment of pellagra and decided to use the drug clinically in the treatment of multiple sclerosis, in an attempt to produce hyperemia in the blood vessels of the central nervous system. On an empiric basis, vitamin B_1 was administered because it restores the ability of the nervous system to carry out carbohydrate metabolism properly.

Five patients with advanced multiple sclerosis were given nicotinic acid, at first intravenously but later intramuscularly, in doses of from 80 to 140 mg. two or three times a week. In the early trials, thiamine chloride, 10,000 international units, was given at the height of cutaneous hyperemia. The ultimate manner of administration was an intramuscular injection of 10 cc. of the solution, each cubic centimeter containing 12 mg. of nicotinic acid and 3.32 mg. of thiamine chloride. To promote development of hyperemia and flushing of the skin, the solution was heated to 100 F. and the barrel of the syringe was warmed. Skin temperatures were recorded for 2 patients, and cerebrospinal pressure readings were made before and during the reaction. Preparations of the brain and cervicothoracic region of the cord of the cat were made to demonstrate the reaction of the pial vessels to the intramuscular injection of nicotinic acid. The pial vessels were photographed before and five and ten minutes after injection of the drug. These photographs revealed distinct increases in the diameter of the pial arteries and an increased blood flow five minutes after the injection of nicotinic acid.

All 5 patients had received various treatments, including fever therapy, without relief. They have been given nicotinic acid and vitamin B_1 for over a year, and all report improvement. When the drugs were discontinued relapse occurred. Although all patients had improved, there were no complete remissions. No untoward symptoms were encountered; electrocardiographic studies and laboratory tests gave normal results. The skin temperatures showed a rise of from 0.5 to 4.5 C. (0.9 to 8.1 F.), depending on the location of the thermocouples, and the cerebrospinal fluid pressure showed a sustained rise coincident with flushing of the skin.

BECK, Buffalo.

EVALUATION OF THERAPY IN MYASTHENIA GRAVIS. NATHAN S. SCHLEZINGER, Arch. Int. Med. **65**:60 (Jan.) 1940.

Schlezinger attempts to evaluate the efficacy of the various drugs used in the treatment of myasthenia gravis in a group of 7 cases in which the diagnosis was clearly established. The following drugs were administered: aminoacetic acid, ephedrine, a combination of aminoacetic acid and ephedrine, anterior pituitary extract (antuitrin), prostigmine and a combination of prostigmine and ephedrine. Whenever possible, a control period of one month without medication was observed, and the drugs were given for the same period. When prostigmine was administered parenterally, examination was made one hour after the injection, but for all other types of therapy examination was made at 9 a. m. The doses of the drugs were as follows: aminoacetic acid, 10 Gm., three times a day; ephedrine, 0.03 Gm., three times a day; anterior pituitary extract, 1 cc. by hypodermic injection twice a day and prostigmine bromide, 90 to 165 mg. in divided doses, three to four times a day by mouth. The test procedures were standardized as much as possible, and an attempt was made to eliminate the factor of cooperation of the patient. Each test was done twice, the maximum figure being taken for comparison. All dynamic tests were timed so that the speed of performance could be standardized. Protrusion of the tongue proved to be the only reliable method of testing the strength of the bulbar muscles, and the term dynamic lingual test was applied to repetitive forced protrusion of the tongue at a definite rate of speed until weakness prevented protrusion beyond the margin of the lips. The static

arm test consisted of continuous abduction of the extended arm while holding 1,000 Gm. 84 cm. above the floor, and the static leg test consisted of maintaining the elevation of the extended leg above a level of 43 cm. from the floor. Dynamic arm and leg tests consisted of repetitive extensions at a fixed rate of speed until weakness set in. The dynamometer was used to test the hand grip and also to determine the duration of the effect of administration of prostigmine.

Ephedrine seems to have a greater effect on the muscles innervated by the spinal nerves. Prostigmine, given either parenterally or orally, was found to be of greater value for muscles innervated by the cranial nerves. The effect of the drug lasts a few hours; it must be repeated at various intervals. The degree of benefit varied with different patients, and the most striking effect was noted when prostigmine was administered parenterally. The combined use of ephedrine and prostigmine was more effective than administration of prostigmine alone. Potassium chloride was of some benefit, but toxic manifestations occurred frequently. Anterior pituitary extract and aminoacetic acid were of no benefit. Schlezinger emphasized that along with medication, hygienic treatment, such as adequate rest and a nourishing diet, should be employed.

BECK, Buffalo.

INSULIN SHOCK THERAPY IN KORSAKOFF'S PSYCHOSIS. P. C. TALKINGTON and T. H. CHEAVENS, J. Nerv. & Ment. Dis. **91**:175 (Feb.) 1940.

Talkington and Cheavens report the case of a woman aged 34 with a marked schizoid personality who became progressively addicted to alcohol. Her sexual adjustments had been unstable, and a firm homosexual attachment had existed for a year prior to admission. She was delirious and exhibited maniacal excitement, with a coarse tremor of the whole body, incontinence and subsultus. There was advanced peripheral neuritis. Despite treatment with sedation and vitamin B_1, the picture of delirium tremens persisted for ten days, with gradual failure of the patient's general condition. Treatment with insulin, begun with doses of 10 units, which were increased to 40 units, produced deep "wet shocks," and the patient's condition slowly improved for two and a half months, after which she was apparently normal. Talkington and Cheavens believe that this form of therapy should also be utilized in the more chronic forms of alcoholic psychosis.

MACKAY, Chicago.

TREATMENT OF NEUROANEMIC SYNDROME IN PERNICIOUS ANEMIA BY VITAMIN B_1. F. SCICLOUNOFF and M. NAVILLE, Schweiz. med. Wchnschr. **70**:166 (Feb. 24) 1940.

According to Sciclounoff and Naville, the cure of pernicious anemia is not always accompanied by disappearance of the neurologic complications. They administered thiamine chloride to 13 patients with the neuroanemic syndrome of pernicious anemia. In the majority of the cases the erythrocytes had reached values of 5,000,000 and up and yet the neurologic symptoms had not been ameliorated. The results obtained by the authors indicate that vitamin B_1 ameliorates and often cures the neurologic disturbances. However, the therapeutic effects are not in proportion to the gravity of the clinical symptoms; besides grave conditions which are completely and quickly improved, there are mild clinical symptoms which are only slightly improved or are completely refractory. The favorable effects become manifest by improvement in the motility and the sensitivity. The painful paresthesias often cease completely and quickly. The abolished reflexes may reappear. In 8 of the 13 cases the results were favorable; in 5 the treatment failed. The daily doses varied between 4 and 10 mg. The duration of the treatment was usually about three weeks, although the patients were often improved after the first week.

J. A. M. A.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

RICHARD B. RICHTER, M.D., *President, in the Chair*

Regular Meeting, Feb. 15, 1940

Development of the Nervus Terminalis in Man. MR. ANTHONY A. PEARSON (by invitation).

The ganglion terminale is formed in part by the migration of cells and fibers from the medial border of the olfactory placode in the region of the anlage of the vomeronasal organ. These cells form groups along the medial border of the olfactory nerve. The migration of these cells continues until one end of the ganglion terminale lies in contact with the ventromedial wall of the forebrain. There is some evidence that cells migrate from the forebrain into the ganglion terminale. This migration may explain the origin of the sympathetic ganglion cells in the ganglion terminale. With further development and differential growth, the ganglion terminale becomes separated from the wall of the forebrain. The connection with the forebrain is retained by fiber bundles which leave the caudal end of the ganglion and enter the forebrain in that region.

In the youngest embryos studied, the fibers of the nervus terminalis pass to the ventral wall of the forebrain, grouped in small bundles. The number of fibers increases until the nervus terminalis enters the brain in a broad stream of fibers. In older embryos, about six nerve bundles constitute the central roots of the nervus terminalis. The bundles course caudad from the ganglion terminale close along the medial border of the olfactory bulb and stalk. The roots of the nervus terminalis penetrate the ventromedial surface of the forebrain just caudal to the attachment of the olfactory stalk. The larger and more medially placed bundles course in the brain close to the surface for some distance. Some of these fibers reach the septal region of the brain.

The nervus terminalis is often differentially stained in pyridine-silver preparations. This makes the course of the nervus terminalis distinct from that of other nerves in this region. From the rostral end of the ganglion terminale a branch is given off which is distributed to the anterior region of the nasal septum. Some of the fibers are distributed to its epithelium. Bipolar ganglion cells migrate from this epithelium and become located along the course of the nerve. Some of these nerve cells retain their connection with the epithelium. Several nerve bundles leave the ventral border of the ganglion terminale and follow the branches of the vomeronasal nerve. Ganglion cells are scattered along the course of all the peripheral branches of the nervus terminalis.

The consensus is that the nervus terminalis is functional in mammals and that there are sensory and autonomic components.

DISCUSSION

DR. REUBEN M. STRONG: Over thirty years ago, when Edinger was interested in the idea of an oral sense, he remarked to me that he considered Locy's article one of the most important contributions to the subject. He was interested in the possibility of the nervus terminalis being a part of the mechanism which he thought might exist for perception of stimuli all of which may not use the olfactory, gustatory and trigeminal nerves. So far as I know, this idea has not been confirmed.

Prof. J. F. Huber regarded the nervus terminalis as primarily sympathetic. I am afraid it will be necessary to put it in the list of structures of unknown

function. I have watched this work with a good deal of interest, and it shows what can be accomplished with good technic and good material.

Correlation of Clinical, Electroencephalographic and Pneumoencephalographic Localization of Cerebral Disease. Dr. E. J. Baldes, Dr. Henry W. Woltman and Dr. W. McKendree Craig, Rochester, Minn.

How to analyze the thousand odd encephalograms already accumulated at the Mayo Clinic has become a problem. We decided to begin our orientation by selecting cases in which we had specific information of the existent cerebral lesion, through craniotomy and biopsy or necropsy. The first question, and the only one with which we are now concerned, was: "How far can one trust electroencephalography as a method of localizing cerebral lesions?" We traced with colored pencils, on printed outlines of the brain, the approximate location of the lesions as determined by the various methods of examination (these were illustrated by a moving picture). Such tracings were made in 55 cases. Since it was believed, at least until recently, that the changes in potential obtained through electrodes placed on the scalp arose from superficial lesions, we thought it justifiable to exclude the deep-lying tumors, such as cysts of the septum pellucidum and tumors of the cerebellum and pons. This left 43 cases on which the following data are based.

The electroencepalographic localization was sufficiently accurate for purposes of the surgeon in 86 per cent of cases. In 2 cases the tracings appeared to be normal; in 2 the abnormal focus was wrongly located, although we had no opportunity to seek an explanation for this by more extensive examination, and in 2 cases the report was "doubtful." Of the 43 cases, the clinical neurologic examination was accurate in 81.4 per cent. In 2 cases the neurologic localization was wrong. In 1 of these we were misled by a partial homonomous quadrant defect in the field of vision, which caused us to localize the tumor on the wrong side of the brain, and in the other, guided by impairment in the appreciation of movements of the joints, we were led to localize the lesion in the parietal area, when it was actually in the temporal lobe. In 6 cases the neurologic findings were insufficient to permit localization. In 17 cases pneumoencephalographic examination was included. Of these, the localization was incorrect in 1 and there was insufficient filling in 2.

DISCUSSION

Dr. Herman M. Serota: I wish to add an observation from experience at the Michael Reese Hospital, where an electroencephalograph was installed about three years ago, for experimental purposes at first. For the deep-lying midline tumors, Dr. Grinker devised a so-called hypothalamic electrode two years ago, and this has been used since. In a case of pineal teratoma, extensive delta activity was observed in the basal regions about the diencephalon. The diagnosis was subsequently verified by pneumoencephalographic findings, and finally at autopsy. I believe the usefulness of the hypothalamic electrode is evident in cases of deep-lying midline tumors.

Dr. Percival Bailey: One should not conclude from this presentation that 86 per cent of all intracranial neoplasms can be accurately localized electroencephalographically. In my experience the method is far from being so accurate.

Dr. Loyal Davis: I have had the opportunity to see the moving picture made by the authors on another occasion; the data are interesting in evaluating the electroencephalographic method in the diagnosis of lesions of the brain which may lend themselves to surgical treatment.

I believe that it would be clearer if the presentation were made, first, of cases in which the electroencephalogram showed the presence and localization of a lesion and subsequently no lesion was seen at operation or autopsy, and, second, of cases in which an electroencephalogram gave no evidence of a lesion and later pathologic changes were discovered.

In summarizing cases for physicians who are not well versed in this method, one should be careful not to give the same weight to the encephalographic reading as to more familiarly established and proved diagnostic methods.

DR. ROY GRINKER: I am sure that the authors do not intend to say that the electroencephalogram designates the presence of any particular type of lesion. The electroencephalogram does not indicate the type, but only localizes the lesion. The hypothalamic lead that Dr. Serota mentioned has now been modified so that its insertion need not cause distress. Instead of a needle point, I use a rubber tip containing cotton soaked in a solution of silver chloride. This lead should be valuable in ascertaining the presence of basal neoplasms located in the midline.

DR. L. J. POLLOCK: I should be interested in knowing whether, in Dr. Woltman's experience, there have been instances in which there was no electroencephalographic evidence of tumor and yet such a lesion was present, and, on the other hand, whether there have been cases in which there was evidence of pathologic wave formations but no tumor was present.

DR. A. EARL WALKER: Recently I have had occasion to review the latest 100 cases of tumors of the brain at the University of Chicago Clinics. In 50 of these cases electroencephalographic records were available. In 24 cases the findings were sufficiently clear to warrant Dr. Case's indicating the localization of the tumor. In 18 of the cases a correct diagnosis was made, and in 5 others it was suggested. In only 1 case—that of an early stage of the tumor—was an inaccurate electroencephalographic localization offered, and that error might have been avoided at present. In 26 cases, in 10 of which the tumor was in the posterior fossa, there was insufficient electroencephalographic evidence for localization. Although the location of the majority of these tumors was apparent from clinical examination, in 24 of the 50 cases air studies were made because the examiner was not certain of the exact site of the tumor. In 11 of these cases the electroencephalogram had correctly localized the lesion. In 1 case, in spite of electroencephalographic evidence to the contrary, the posterior fossa was explored when a tumor of the frontal lobe was found. The electroencephalogram, therefore, appears to be a valuable adjunct in the localization of intracranial lesions. It is not diagnostic in every case, but when the evidence is positive the findings are reliable. I believe the accuracy of the electroencephalogram will depend on the criteria used by the interpreter.

DR. EDMUND JACOBSON: Will the authors tell how the outlines of the lesions were determined? Were the photographs representative of most of the work or were the electrodes moved about? I wish to ask also about the size, material and other characters of the electrodes.

DR. HENRY W. WOLTMAN, Rochester, Minn.: The criticisms and observations are well taken. I am not sure I can recall all of them. A true appraisal of the clinical value of electroencephalography should, of course, include its use in cases of tumors lying in the midline. If this were done, the favorable impression I gave of the value of electroencephalographic localization would suffer. For the time being we thought we might be justified in excluding such tumors. A number of electroencephalograms made in cases of deep-lying lesions, most of which were tumors, were either normal or showed bitemporal disturbances and a tendency to polar localization, that is, in the front or in the back of the head. In a few instances we employed nasal electrodes, the technic of using which we learned from Dr. Grinker, but this was not done routinely. We have reason to think it will be helpful. A complete survey should take into account all the electroencephalograms that were made, but only in the limited number of cases I am presenting did we have data concerning the underlying lesion.

In this series there were 4 cases in which electroencephalograms were not of value. In 2 cases, although the patient had a superficial tumor of the brain, the tracings were reported as normal, and in 2 cases the disturbance was wrongly localized. Since this analysis was made similar cases have occurred.

In the series of cases presented, ten placements of electrodes were made, and in some instances they were moved about. For some patients we now use twenty-five electrodes, although this is time consuming for routine work. The electrodes were of silver, coated with silver chloride, and were 0.5 cm. in diameter. They were fastened in place with collodion, and into the small cup there was placed a mixture of tragacanth, water, glycerin, sodium chloride, hydrochloric acid and boric acid.

To be sure, electroencephalography is only one method of examination; if not correlated with other methods it would in most of our cases have been of little value. Taken as a part of the examination, we believe it is helpful.

Anatomic Relations of the Hypophysial Stalk and the Median Eminence. DR. THOMAS A. WEAVER JR. (by invitation).

The results of a cytologic study of the hypothalamicohypophysial region of 9 normal monkeys and 4 normal cats are presented and appropriate lantern slides shown. The median eminence is defined as that portion of the hypophysial stalk that begins almost immediately posterior to the optic chiasm and extends posterosuperiorly to the point where the stalk forms an angle with the anterior limit of the premamillary recess of the third ventricle. Inferiorly, the median eminence terminates at the point where the straight portion of the hypophysial stem clearly begins.

The lateral margins of the median eminence are not demarcated by any distinct anatomic structure, as are the anterior and posterior limits. However, the lateral margins are no less definite. Just posterior to the optic chiasm the lateral borders of the median eminence are in contact with the posteromedial margins of the supraoptic nuclei. Further posterior the lateral margin forms an acute angle with the floor of the lateral portion of the hypothalamus.

The median eminence was examined for its cytologic constituents, it being borne in mind that the neurohypophysis contains a characteristic glia cell, the pituicyte, which is not found elsewhere in the central nervous system, and that ganglion cells, oligodendroglia and microglia, all normal constituents of the hypothalamus, are not observed in the neurohypophysis. The study showed that most of the posterior portion of the median eminence contains pituicytes and is closely related to the neurohypophysis, whereas in much of the anterior portion of the structure typical hypothalamic elements are seen. Hence, much of the anterior portion of the median eminence must be considered a part of the tuber cinereum of the hypothalamus.

It was pointed out that in experiments designed to divide the greater part of the neurohypophysis from the hypothalamus, in the study of diabetes insipidus, careful attention should be given to the anatomic junction of these two structures.

DISCUSSION

DR. PERCIVAL BAILEY: As Dr. Weaver has said, a great deal of neurohypophysial tissue must have been left attached to the base, at least in experiments on monkeys. As is known from previous experience, the hypophysial stalk is not as evident and not as easy to sever in the cat and dog as in the monkey. As Dr. Weaver has demonstrated, in the monkey it is severed considerably below the hypothalamic-hypophysial junction.

Diagnosis, Localization and Treatment of Intracranial Saccular Aneurysms. DR. MAURICE N. WALSH, Rochester, Minn.

It was formerly supposed that both the clinical diagnosis and the treatment of intracranial saccular aneurysms were impossible. More has been learned of this problem; now aneurysms in certain locations which are large enough to produce signs and symptoms of compression can be localized and treated. It is not suffi-

cient to locate the aneurysm with reference to adjacent nerve structures; successful surgical treatment depends on accurate knowledge of the artery from which the aneurysm arises.

Most intracranial aneurysms occur at the base of the brain. They have been divided into an anterior and a posterior group, depending on their position in relation to the cerebral circulation. The anterior group represents the largest number of aneurysms. Aneurysms in the anterior portion of the circle of Willis and adjacent vessels, comprising largely that portion of the cerebral circulation supplied by the carotid artery, are most amenable to surgical treatment, and my discussion is limited to the aneurysms of this group.

Most saccular aneurysms are thought to arise from an area of congenital weakness at the point of junction of the arteries at the base of the brain. This weakness is stated to be due to a developmental defect in the muscle of the arteries at this point. Arteriosclerotic aneurysms probably come next in frequency to those of congenital origin, while embolism and syphilis are rarely causes of intracranial aneurysm.

The incidence of intracranial aneurysms in the population is difficult to determine. They are not infrequent, however, in neurologic practice. Dott has estimated that they are observed in about 1 of 700 autopsies.

It is erroneous to speak of all aneurysms as occurring in the circle of Willis. MacDonald and Korb demonstrated that the largest single group of aneurysms occurs on the middle cerebral artery beyond the circle of Willis, although most intracranial saccular aneurysms arise from vessels of the circle of Willis. MacDonald and Korb found that aneurysms which had ruptured were three times as frequent on the anterior part of the circle of Willis as on the posterior part.

There are two groups of symptoms and signs which may be caused by intracranial aneurysms. The first includes those due to direct pressure on surrounding nerve structures, particularly the cranial nerves. These are the so-called neighborhood signs. The second group includes those due to leakage from the aneurysmal sac, with the production of the well known syndrome of subarachnoid hemorrhage. Subarachnoid hemorrhage is almost always due to rupture of an intracranial saccular aneurysm. Rarely, it may be due to rupture of vessels in a tumor of the brain, such as hemangioma, or to hemorrhagic encephalitis. Most intracranial aneurysms do not give localizing or lateralizing signs of value previous to the fatal rupture. It is probable that less than one third of patients with intracranial aneurysm have signs which permit localization or lateralization of the lesion. The symptoms and signs produced will depend on the location and size of the aneurysm and whether or not it has ruptured.

From a review of the literature, I believe that the only characteristic syndrome produced by intracranial aneurysms is that which is associated with an aneurysm in the cavernous sinus below the bifurcation of the internal carotid artery. This was described by Foix as a syndrome of the lateral wall of the cavernous sinus. It consists essentially of pain, and often anesthesia, in the distribution of the first division of the fifth nerve, palsy of the third nerve, frequently paralysis of the muscles supplied by the fourth and fifth cranial nerves and sometimes exophthalmos. A bruit is rare. Evidence of compression of the optic nerves, chiasm or tracts may be present, and after rupture changes in visual fields the characteristic of interruption of the optic radiation may be found if there is extensive damage to the brain. Palsy of the third nerve alone, however, is not of localizing significance, as it may result from aneurysms situated on any of the basilar arteries, even outside the circle of Willis. Next to aneurysms located in the cavernous sinus in frequency of production of cranial nerve palsies are those at the junction of the posterior communicating artery and the internal carotid artery. It is estimated that 47 per cent of such aneurysms will give rise to palsy of the third nerve. Aneurysms below the bifurcation of the internal carotid artery are referred to as infraclinoid aneurysms.

Differential diagnosis must include meningiomas of the inner third of the sphenoid ridge, or meningiomas arising from the dura overlying the gasserian ganglion, and arteriovenous aneurysms in this location. Diagnosis of an unruptured intracranial aneurysm is possible, but difficult. Roentgenograms of the head may reveal unilateral sellar erosion, erosion of the superior orbital fissure, calcification of the aneurysmal wall, enlargement of the carotid canal or sellar enlargement.

Aneurysms may be of several years' duration and may become very large. When subarachnoid hemorrhage is present the picture may be confused, and false localizing signs may occur. Arteriograms with colloidal thorium dioxide have been of value in localizing intracranial aneurysms. They have the added advantage of giving information regarding the cerebral circulation. There has been some discussion of the danger of obtaining arteriograms with thorium dioxide.

Treatment of intracranial aneurysms, when they can be localized, is surgical. Such treatment is most successful in cases of infraclinoid aneurysms. In a large percentage of the reported cases ligation of the homolateral internal carotid artery has been successful. Dandy recently treated 4 patients, 1 by intracranial exploration with clipping the neck of the aneurysm and electrocoagulation, and 3 by "trapping" the aneurysm between intracranial ligations and later ligating the artery in the neck. Before ligation of the internal carotid artery is attempted, it should be ascertained by digital compression of the artery in the neck that the collateral circulation through the circle of Willis is adequate.

At the Mayo Clinic the internal carotid artery has been ligated in the neck in 8 cases of intracranial aneurysm. All the patients have had relief from symptoms and signs due to the aneurysm, while none have had further subarachnoid bleeding.

There will probably always remain cases in which accurate diagnosis and localization of the aneurysm cannot be accomplished in time to permit surgical treatment, but the former pessimistic view of the hopelessness of all intracranial aneurysms is no longer tenable.

DR. JOHN MARTIN: I wish to make a few remarks concerning Dr. Davis' series of aneurysms of the intracranial portion of the internal carotid artery and tumors of the gasserian ganglion and its sheath. In some of the cases the diagnosis of trigeminal neuralgia had been made previously. Approximately half the patients had a tumor, the other half an aneurysm. In each case in which an aneurysm was found the onset of symptoms was more sudden, and there was more constant involvement of the third, fourth and sixth nerves than in the cases of tumor of the paratrigeminal area. Invariably, the pain was more marked in the ophthalmic division of the fifth nerve, or was even limited to it, but the pain with either aneurysm or tumor was less excruciating than that of trigeminal neuralgia. An important differentiating point was that in cases of tumor of the gasserian ganglion there tended to be patchy areas of hypesthesia over the face, while this was not true in cases of aneurysm. One came to realize that a careful examination is needed to differentiate tumor and aneurysm when a lesion of the paratrigeminal area is in question.

DR. PERCIVAL BAILEY: I judge that Dr. Walsh used the arteriographic method very little; yet it demonstrates such lesions beautifully. I wish to ask him why he did not use this method more frequently.

DR. R. P. MACKAY: The syndrome associated with aneurysms of the anterior portion of the circle of Willis, as outlined by Dr. Walsh, reminds one of so-called ophthalmoplegic migraine. Has Dr. Walsh found anything in the history in these cases which might have led to a mistaken diagnosis of ophthalmoplegic migraine?

DR. MAURICE A. WALSH, Rochester, Minn.: In reply to Dr. Bailey: The arteriographic method has been little used at the clinic; it was attempted in 3 cases in this series, and in only 2 were any changes demonstrated. In 1 case, unfortunately, the picture was not good enough to demonstrate, and in the other

the anterior cerebral artery did not fill. At the clinic there is not the proper apparatus for cerebral arteriography.

With respect to thorium dioxide, Matas stated that with the small doses of thorium used no reports of toxic reactions have been made. Toxic effects have been reported when larger amounts were used. In Dandy's opinion the less done to the patient the better. He discouraged the use of thorium dioxide. It is to be hoped that some preparation of iodine may be successfully used in place of this substance.

Dr. Mackay's question about ophthalmoplegic migraine is important. There has been much written on this subject. Most patients gave a history of headache of migrainous type for several years. It was thought that this might indicate the existence of the aneurysm for some time. In many cases what was called migraine or migrainous neuralgia proved to be intracranial aneurysm at autopsy.

RICHARD B. RICHTER, M.D., *President, in the Chair*

Regular Meeting, March 21, 1940

Familial Progressive Spinal Muscular Atrophy: Report of a Case. DR. VICTOR E. GONDA.

I shall report 2 cases of progressive spinal muscular atrophy which occurred in a mother and an adult daughter; this incidence makes the cases of increased interest, since this syndrome is usually limited to children.

The daughter at the age of 30 first noticed that her right hand had become awkward in executing finer movements, especially in playing the piano. Two years later she noticed that her left hand had also become clumsy. As far as could be determined, she had not suffered from any major ailments. She was the mother of 2 healthy children. Her younger sister was suffering from a severe anxiety neurosis.

Twenty-seven years ago, the mother, when she also was 30 years of age, first noticed weakness and awkwardness of movement in the right hand; four years later these symptoms appeared in the left hand also. She did not seek medical help. Ten years later her ankles became weak and "turned" on walking.

In many ways the physical findings were similar in the 2 cases; they varied only in the degree of involvement. In neither case could one detect the slightest impairment of the cranial nerves. It must be emphasized that the bulbar group of nuclei was not involved. There was considerable loss of volume of the intrinsic muscles of both hands, more pronounced in the hands of the mother. In both cases the muscles of the right hand showed more advanced atrophy. The thenar eminence and the interosseous muscles of the right hand were more flattened than those of the left. Approximation of the fingers was executed slowly and with little strength, but apposition of the tip of the thumb to the tip of the little finger could not be performed at all. The hand grip and the active movements of the wrist, elbow and shoulder joint were surprisingly well preserved in both cases. I could not detect any atrophies other than those described. The biceps, triceps and radial reflexes could be elicited in the daughter, but except for the left triceps reflex all were absent in the mother. The knee jerk was easily elicited in both patients. The mother had bilateral foot drop with absence of the ankle jerk and plantar response; the daughter had no complaints with reference to the lower extremities and was able to walk long distances and dance for hours without becoming fatigued; her ankle reflexes, however, could not be elicited at all. This fact, I think, is of great significance.

There were no sensory changes in either patient. The usual laboratory findings were normal. Roentgen studies of the cervical vertebrae showed no pathologic changes.

Electrical examination revealed complete reaction of degeneration of the opponens pollicis and the first interosseous muscle of the right hand of the mother. The other small muscles of the hand showed partial or mixed degeneration. The muscles of the forearm, arm and lower extremity revealed no electrical changes.

There were no signs or symptoms of involvement of the corticobulbar or corticospinal neurons. There was no pseudohypertrophy.

These 2 cases, then, can be classified as instances of progressive spinal muscular atrophy of the Aran-Duchenne type, occurring in a mother and daughter. Except in the degree of involvement, they are photographic copies of each other.

It is well known that the occurrence of familial muscular atrophy is practically limited to children. A review of the pertinent literature reveals reports of only a few cases of the disease in adults, and none of hereditary occurrence. Wechsler (A Textbook of Clinical Neurology, Philadelphia, W. B. Saunders Company, 1931, p. 192) stated that progressive spinal muscular atrophy may be familial but never hereditary. As far as I can discover, this case is the first in which the condition occurred in a mother and daughter in such pure form.

In 1 of the present cases the disease is of twenty-seven years' duration and is still limited to the spinomuscular neurons, without the slightest involvement of the bulbar group of nerves or of the pyramidal tracts. This fact is of importance because it is now generally believed that progressive bulbar palsy, progressive spinal muscular atrophy and amyotrophic lateral sclerosis are all one disease of the motor system and need not be differentiated as disorders of independent origin.

These diseases, hitherto, have not yielded to any kind of treatment. Recently, however, Bicknell (*Lancet* **1**:10 [Jan. 6] 1940) reported recovery in 2 cases of amyotropic lateral sclerosis, in 1 of which the disease was of six years' duration, following treatment with vitamin E. Wechsler (Recovery in Amyotrophic Lateral Sclerosis Treated with Tocopherols [Vitamin E]: Preliminary Report, *J. A. M. A.* **114**:948 [March 16] 1940) reported almost simultaneously 2 cases of amyotrophic lateral sclerosis in which there was prompt response to vitamin E therapy administered in the form of synthetic tocopherols.

The younger patient, whom I have treated since November 1939 with large doses of vitamin B complex, already shows definite signs of improvement. Encouraged by success so far and by the optimistic reports of Bicknell and Wechsler, I shall give these patients larger doses of vitamin E and smaller doses of vitamin B, with the hope of recovery.

DISCUSSION

DR. PERCIVAL BAILEY: I should like to ask whether Dr. Gonda does not think twenty-seven years a long duration of progressive muscular atrophy, with no greater extension than in these cases. While anatomically the diagnosis may be correct, at least in so far as the syndrome is concerned, I wonder whether one may not be dealing with a pathologic entity different from Charcot's disease.

DR. VICTOR E. GONDA: In reply to Dr. Bailey, there are cases in which the disease has lasted much longer without the vital centers being involved.

Use of High Voltage Roentgen Rays in Treatment of Intracranial Gliomas.

DR. HAROLD C. VORIS.

Irradiation has been used in the treatment of intracranial tumors almost since the beginning of the present century. The effect of irradiation on the gliomas has been studied more thoroughly than that on any other group of intracranial tumors. Ewing's prediction, in 1921, that tumors exhibiting marked anaplastic tendencies would be more radiosensitive was the foundation of the hope that irradiation of the gliomas would prove uniformly successful. Unfortunately, this did not prove to be the case.

Practically all authors have emphasized the importance of preliminary exploration with biopsy, if possible, and decompression before irradiation is begun. The

reasons for advocating preliminary operation are well recognized: 1. One otherwise may be dealing not with a tumor but with some condition simulating a neoplasm. The neurosurgeon is all too familiar with various lesions causing the syndrome of so-called pseudotumor. 2. Clinical localization may be at fault and may be corrected only by surgical exploration. 3. Exploration may disclose the lesion to be one that has a good operative prognosis but is resistant to roentgen rays. If such a lesion is given a therapeutic trial of irradiation, as advocated by some enthusiastic roentgenologists, valuable time will be lost and an otherwise operable tumor may become inoperable. 4. Partial or subtotal removal of the tumor or decompression will give relief from symptoms until the effect of irradiation can be obtained, and will provide for the relief of increase in intracranial pressure due to the effects of roentgen rays.

The question of the relative value of radium and of high voltage roentgen rays has been much discussed. The greater technical difficulties and dangers associated with the use of radium and the progress made in improvement of the technic of the use of high voltage roentgen rays have practically resolved the problem in most clinics in favor of roentgen ray therapy. Modern technic makes it possible so closely to approximate the gamma ray of radium, even at a considerable depth, that there is apparently little practical advantage in the employment of radium to offset the greater difficulties of its application, especially its interstitial application.

The normal brain can be damaged by radiation, although with the ordinary therapeutic doses such damage must be minimal. In patients intensively treated and surviving for long periods, the possible late effects must be kept in mind. Some authors, notably Beclere, have stated that irradiation diminishes the formation of cerebrospinal fluid and thus relieves increased intracranial pressure even when the tumor itself is not radiosensitive. However, if this were true, irradiation would be a valuable treatment for idiopathic hydrocephalus, when, as a matter of fact, it is of no value.

There is fairly uniform agreement that the medulloblastoma is the most radiosensitive of gliomas. I have personal knowledge of 2 cases of medulloblastoma of the cerebellar vermis in which intensive high voltage roentgen treatment was administered to the cerebellum and routine treatment was applied to the spinal canal and the cerebrum. When signs of recurrence developed, additional treatment was given to the cerebellum. Necropsy in both cases showed that death was due to tumor implants in the cerebral hemispheres, in 1 case in the lateral ventricles and in the other in the cerebral subarachnoid spaces. In neither case was there local recurrence in the cerebellum. In 1 case there was no gross evidence of tumor in the posterior fossa; in the other only a small nodule was present in the fourth ventricle. The importance of thorough irradiation of the entire cerebrospinal axis cannot be overemphasized in cases of medulloblastoma. This is not necessary with other gliomas, as medulloblastoma is the only one to spread by implants.

Some authors have reported considerable change in ependymomas as a result of irradiation; others have reported them to be highly resistant to this treatment. The same discrepancy is present in reports of the effects on glioblastoma multiforme.

In case of the astrocytomas, oligodendrogliomas and polar spongioblastomas there is little evidence of clinical benefit or histologic change as a result of irradiation.

As already mentioned, many reports emphasize the clinical improvement or the increased period of survival following irradiation, but fail to take into account differences in location and size of the tumor, in extent and type of surgical procedure, in histopathologic interpretation from one clinic to another and in technic and dosage used in treatment. My knowledge of the last factor is second hand, but it is obvious from the literature that the variations in this factor equal, if they do not exceed, those in the others mentioned.

The present trend in all but a few clinics is to administer high voltage roentgen rays in fractional doses through multiple portals in much larger total amounts than in the past. Doses of 150 to 250 roentgen units given daily through as many alternate portals as possible for a total of at least 5,000 roentgen units, with repetition of the course in from three to six months in cases in which the tumor is known to be radiosensitive or shows clinical improvement, is the method used at the Mercy Hospital Institute of Radiation Therapy.

The dangers of irradiation may be listed as (1) injury to the skin, (2) radium osteonecrosis, (3) depilation, (4) sloughing or delayed healing of the operative wound, (5) injury to normal brain tissue and (6) reactions to treatment. Damage to the scalp or bone and sloughing or delayed healing of the wound should not occur in the hands of competent roentgenologists. However, it is wise to allow primary healing of the operative wound before commencing irradiation. Loss of hair is unavoidable, and with adequate treatment will in most cases be permanent. Its importance, of course, is negligible as compared with the benefit from successful treatment. Injury to normal brain tissue has already been discussed and must be kept in mind, particularly with the present tendency to increasingly large doses of radiation. Reactions to treatment are probably usually due to edema or vascular changes in the tumor. Preliminary decomposition is of great value in preventing them or in mitigating their severity. However, at times it may be necessary to administer hypertonic solutions intravenously or to perform spinal or ventricular drainage in order to counteract symptoms of increased intracranial pressure during or following irradiation. Again, the spacing of treatments several days apart may be of value in preventing adverse reactions.

In conclusion, it may be stated that irradiation cannot be substituted for surgical procedures in the treatment of gliomas. In the case of certain tumors, such as medulloblastoma, it not only may keep the growth under control but may even offer promise of cure. It is of no value for astrocytoma, oligodendroglioma or polar spongioblastoma. Glioblastoma multiforme or ependymoma may show some favorable clinical response. There is no evidence that the formation or absorption of cerebrospinal fluid is influenced by irradiation.

In the present stage of knowledge, exploration with decompression and biopsy, if possible, should precede irradiation.

DISCUSSION

DR. PERCIVAL BAILEY: This seems to be a judicious summary. I might say that spongioblastomas are sometimes radiosensitive. One sees this in cases of pontile tumors with involvement of the cranial nerves in children. In several such instances I have secured marked improvement, rapid although temporary. One should be cautious about renewing irradiation when symptoms recur. It is known that marked degenerative changes are provoked in the central nervous system when one gives as much as 18,000 to 20,000 roentgen units. I have never seen anything gained by increasing the radiation above 4,500 roentgen units. With such high doses one is more apt to provoke sclerosis and degeneration of the brain than to cause regression of the tumor.

If one could isolate the tumor from the nervous system one could give enough radiation to destroy it. Unfortunately, the brain must be considered; if it is given too much radiation destruction of the tissue will result. The only case I have had in which the tumor could be directly irradiated was that of a very malignant glioma, proved by biopsy, which extended to the surface in Broca's area. Intensive irradiation was directed solely to this region; I do not remember the dose, but it produced weeping eczema of the overlying scalp for many months. It has been about five or six years since this treatment was given, and there have been no signs of recurrence of the tumor in a location in which any recurrence would have caused immediate difficulty in speech.

DR. A. EARL WALKER: Another disadvantage of roentgen therapy is the increased danger of infection. This is particularly true if one is contemplating a

secondary craniotomy. Dyke (*Am. J. Roentgenol.* **43**:225, 1940) stated that 5 of the 31 patients given radiation in the operating room at the New York Neurological Institute died as a result of severe infections of the wound. This danger has also recently been emphasized in a report from Philadelphia on intracranial complications following irradiation for carcinoma of the scalp (Pendergrass, E. P.; Hodes, P. S., and Groff, R. A.: *Am. J. Roentgenol.* **43**:214, 1940).

Dr. Harold C. Voris: With respect to the large amount of radiation, the patient in case 3 had two recurrences, one in 1936 and one in 1939. On both occasions he received approximately 5,000 roentgen units, with definite relief of symptoms. He had received about the same amount the first time. I am sure that this man has had too much irradiation for the good of the brain and that the mental deterioration is related to the roentgen treatment. On the other hand, three doses of roentgen rays at different times has given definite relief from aphasia and hemiplegia on each occasion.

Paraphysial Cysts Arising from the Anterior Portion of the Roof of the Third Ventricle: Clinical and Pathologic Review of Six Cases. Dr. Howard Zeitlin and Dr. Ben W. Lichtenstein.

We shall review 6 cases of cystic tumors of the third ventricle and discuss briefly the symptoms, pathologic features, origin and ventriculographic findings and the probable mechanisms of death. Such cysts do not cause early symptoms. Because of their site of origin, they tend to block the passage of the cerebrospinal fluid from the lateral ventricles into the third ventricle. By a ball and valve action, blocking the fluid, and the impaction of the cyst into the foramins, the most characteristic symptom is produced, namely, sudden onset of severe headaches. As the cyst enlarges it compresses the hypothalamic nuclei, giving rise to hypersomnolence or drowsiness, somewhat similar to physiologic sleep. Other symptoms of hypothalamic origin may also be present. Visual disturbances due to pressure on the optic chiasm and the optic nerves and to increased intracranial pressure commonly occur. The walls of the thalamus become compressed, frequently giving rise to paresthesias in the extremities and weakness in the legs. If the cyst should suddenly become impacted in the foramens of Monro, epileptiform seizures usually result.

Arising in the roof above the tela choroidea, the cysts are limited in growth upward by the pillars of the fornices and usually sag by their own weight through the thin membranous roof. As a pedicle, they may have the tela alone or the tela and the choroid plexus, which is attached to the superior lateral surface of the cyst. In this manner the cyst may swing like a pendulum, giving the characteristic intermittent symptoms of headaches, particularly on change of position of the head.

Certain factors support the premise that these cysts arise from specific structure, such as the paraphysial gland. 1. The cysts arise from a particular point in the most anterior portion of the roof of the third ventricle. 2. Microscopically and macroscopically, because of their colloid-like contents, they differ from any other cyst arising in the brain or from the ependyma. 3. The ependyma-like cells lining the cyst contain lipochrome granules in their cytoplasm. MacLean showed that similar lipochrome granules occur in lower vertebrates in the anterior fifth of the roof of the third ventricle, which was identified as the paraphysis. Posterior to the latter region in the roof plate of ependymal lining cells no pigment was seen. 4. Ependymal lining cells frequently appear as actively secreting cells. 5. The structure of the tubules is fairly similar to that of the paraphysial gland of lower vertebrates, and their presence suggests origin from a glandular structure. The paraphysial gland in Sphenodon (a lower vertebrate) reveals, according to Dendy, the formation of a complicated glandlike structure of numerous small anastomoses of tubules consisting of a single layer of ependyma-like cells with interlacing small

blood vessels. The tubules are similar to those observed in the cyst wall in 3 of our cases.

Possibilities of the mechanisms of death in cases of this tumor are: (1) blocking of the cerebrospinal fluid, with resulting hydrocephalus and increased intracranial pressure; (2) pressure at the point of origin of the vein of Galen within the roof of the third ventricle, resulting in stoppage of the return flow of blood from the choroid plexus, as mentioned by Stookey; (3) sudden pressure or destruction of important vital centers in the hypothalamic region and in the walls about the foramens of Monro that are concerned with the mechanisms of visceral functions.

DISCUSSION

DR. ARTHUR WEIL: In 1931, Dr. Haven and I studied 3 cases of these colloidal cysts of the third ventricle, 1 of which I reported before this society (Colloid Cyst of the Third Ventricle, ARCH. NEUROL. & PSYCHIAT. **28**:726 [Sept.] 1932). In 2 cases the cyst was adherent to the roof of the third ventricle; in 1 case it was pedunculated. In all 3 cases there was evidence of mentingitis of the overlying tela choroidea, intermingled with the remains of old homorrhages and granulation tissue formed around fatty debris. Furthermore, there was encephalitis in the surrounding hypothalamus and thalamus, with mild perivascular round cell infiltration and the formation of foci of proliferated glia and neuronophagia. In the case which I reported the encephalitis, which had the histologic characteristics of the epidemic type, involved the midbrain and the rest of the brain stem.

Granted that these cysts arise from embryonic rests of the paraphysis or the anlage of the ependymal covering of the choroid plexus, the question arises whether an inflammatory process could not have been an essential contributing factor in their formation. The fact that they all arise at the same place, the junction of the tela choroidea with the lower surface of the fornix, also suggests the possibility of the spread of a local inflammatory process to the choroid plexus or the accumulation of metabolic waste products at this point; this would explain the formation of the localized granulation tissue, which has been described, at the upper surface of the cyst.

In the lantern slides which the authors showed such localized meningitis of the tela choroidea at the upper pole of the cyst was evident, although special attention was not called to it. I wish to ask whether the authors found encephalitis also in the hypothalamus or in the rest of the brain in their 6 cases.

DR. W. H. SWEET: Is there any evidence that the paraphysis, in those species in which it is well developed, secretes a substance similar to the colloid seen in these cysts?

DR. ABRAHAM ETTLESON: I wish to ask whether any patients had attacks of cataplexy. Dr. Zeitlin stated that removal of the colloid and excision of a portion of the capsule should be sufficient in treatment of these cysts. I wish to know whether that is what he meant or whether it is better to remove the whole cyst at the time of operation.

DR. HOWARD ZEITLIN: As to the question whether an inflammatory process could have been a contributing factor in the formation of the cyst: In our cases in which the cysts were small, particularly those in which they hung freely from the roof by a pedicle, we found no inflammatory elements in the capsule wall or in the surrounding structures. On the other hand, as in our first and second cases, the large size of the cyst, the long duration of symptoms and the repeated attacks caused a pressure effect on the surrounding structures, resulting in blockage and venous stasis, both of the choroid plexus and of the blood vessels of the cyst wall. The inflammatory reaction is probably the result of the pressure phenomena and the repeated impactions of the cyst into the foramens of Monro. In our cases we did not find evidence of encephalitis in the hypothalamus or in the remaining portions of the brain. The occasional changes seen in the hypothalamic region were thought to be secondary to the continuous pressure phenomena.

As to the question of symptoms occurring only in adults: We have seen these cysts in the roof of the third ventricle in childhood. They are small, and it may take years before the cyst becomes large enough to manifest itself.

In answer to Dr. Sweet's question: Little has been described concerning the detailed microscopic pathology of the paraphysis in lower vertebrates.

The five factors I have mentioned previously to prove the paraphysial origin of these cysts lead one to believe that the origin of these cysts is fairly well established. Actually it is not so. Warren, working on the roof plate of mammalian embryos, pointed out the presence of small tubules, originally seen by Dr. Percival Bailey, just posterior to the paraphysial arch or gland. Likewise, Dextor, in studying the paraphysis in common fowl, noted a small vesicle posterior to the paraphysial arch that was lined by a single layer of cells, and the cavity contained a coagulum. This structure perhaps resembles somewhat the cystic tumor under discussion.

The question has been raised by other authors whether these cysts could arise from the tubules observed posterior to the position of the paraphysis. Because of the controversial nature of this question, I can understand why Dr. Bailey chose the noncommittal term of neuroepithelial cyst in naming these tumors.

Leaving the controversy to be settled in the future, I believe, for all purposes concerned, that it would be best to call these cysts paraphysial cysts arising from a noninvoluted vestige of the paraphysial gland.

DR. BEN W. LICHTENSTEIN: In answer to Dr. Weil's first question as to why a tumor arising from an embryonal rest should make its appearance in adult life, I may say that such a phenomenon is not rare. Cysts arising in the ovaries and the cysts of polycystic kidney many times come from embryonal rests and make their appearance later in life. In answer to Dr. Weil's second question about the inflammatory cause of these colloid cysts, I may say that it is not uncommon to find signs of inflammation in the capsule of these cysts; the compressed and degenerated surrounding brain tissue, too, may show perivascular infiltrations. Such inflammatory changes do not indicate true encephalitis. If these colloid cysts develop secondary to inflammatory phenomena, one should find them elsewhere in the ventricular system. As they arise only in the roof of the third ventricle, I believe they are different from cysts of the ependyma and choroid plexus.

Surgical Treatment of Lead Encephalopathy, with Particular Reference to the Prevention of Sequelae. DR. W. TRACY HAVERFIELD and MISS ANNA S. ELONEN.

Five cases of lead encephalopathy in children with the manifestations of increased intracranial tension are reported. In all 5 cases surgical decompression was made for relief of the increased intracranial pressure; in 2 it was suboccipital and in 3 subtemporal.

In 1 of the cases of subtemporal decompression local anesthesia was used. During the procedure the patient had a generalized convulsion, with cessation of respiration, and died. Had general anesthesia been used this might have been avoided.

One patient was comatose on admission. On subtemporal decompression the temporal lobe herniated to an alarming degree. The patient's condition grew worse, and he died on the fourth postoperative day.

The 3 patients who survived have been followed since the operation, for three, five and seven years, respectively. Two are physically, neurologically and mentally normal. The remaining patient is in perfect health; his mental development is retarded somewhat below the average for his age and below that of his fraternal twin brother; from birth he has outweighed his twin brother, and of the 2 he is the physical superior.

From these cases and from a review of the literature it is concluded that development of the signs of increased intracranial pressure without localizing

symptoms, especially when accompanied by convulsions and/or the signs of meningeal irritation, should suggest lead encephalopathy. Roentgenograms demonstrating lines of increased density at the ends of the metaphyses of the long bones aid materially in this diagnosis.

Surgical decompression of the brain is an effective means of relieving the symptoms of intracranial hypertension in such cases, of preserving life and vision and of preventing the development of sequelae if treatment is not too long delayed.

It appears that either suboccipital or subtemporal decompression is effective and that general, and not local, anesthesia should be used for the procedure.

DISCUSSION

MISS ANNA S. ELONEN: Unfortunately, in the case of the twins no psychometric tests were given before the illness occurred. However, according to the mother, the twins were not as far apart in mental development as they are now, if one is to judge from reports on the time of their walking, talking and general development. The differences shown by the tests are somewhat great, although fraternal twins are expected to vary more than identical twins brought up in the same environment. The interesting point in the results of tests on the two boys is the difference in their performance tests. The normal twin is much better in performance situations than his brother.

DR. R. P. MACKAY: If Dr. G. W. Hall were here, he would wish to mention the case of a young man with lead encephalopathy whose history demonstrates the truth of the authors' thesis. J. J., aged 32, an office employee of the Pullman Company, was brought to Dr. Hall in September 1939 because of a history of alcoholism and convulsions for two months. He was sent to a sanatorium; while there papilledema appeared. He was then referred to the Billings Hospital, where Dr. Percival Bailey attempted a ventriculographic examination and found that the ventricles were collapsed. No hematologic evidence of lead intoxication was found at that time, but anemia subsequently appeared. At St. Luke's Hospital, in November 1939, when the patient was again under Dr. Hall's care, marked basophilic stippling was found on repeated occasions. The papilledema persisted, and bilateral subtemporal decompression was carried out by Dr. Eric Oldberg, on Nov. 16 and Dec. 1, 1939. On Jan. 23, 1940 the urine contained 0.169 mg. of lead per liter. After treatment with calcium gluconate and disodium monohydrogen phosphate (Na_2HPO_4) the lead finally disappeared from the urine, the blood picture became normal and the patient made an uneventful recovery, returning to work about March 1. The source of the lead was not learned; it may have been ingested with the liquor. It seems from this case that decompression is a valuable method of treatment in adults as well as in children.

DR. DAVID SLIGHT: I wish to ask Dr. Haverfield if he can state in what proportion of cases of lead encephalopathy the cerebrospinal fluid pressure is increased. In all his cases the disease affected children, but I seem to recall instances in which adults had the disorder without increase in pressure.

DR. W. T. HAVERFIELD: The case cited by Dr. Mackay is interesting. Thomas and Blackfan, in 1914, were the first in the United States to point out that, while lead encephalitis occurs in both adults and children, it is much more common in children.

Medical management by dehydration and repeated spinal fluid puncture, with removal of fluid, may be sufficient to save life, but if the increased intracranial pressure is not adequately relieved, optic atrophy, hemiplegia and convulsions are among the sequelae that may occur.

In answer to Dr. Slight, it is difficult to give the exact proportion of persons with lead poisoning who show encephalopathy, but I may emphasize that while it is seen in both adults and children it is more common among children, and that in children it is the principal manifestation of lead poisoning.

PHILADELPHIA NEUROLOGICAL SOCIETY

SAMUEL B. HADDEN, M.D., *President, in the Chair*

Regular Meeting, Feb. 23, 1940

Dangers of Subarachnoid Injection of Alcohol for Relief of Pain. DR. F. H. LEWY and DR. ROBERT A. GROFF.

In another state, a man aged 61 had previously received a subarachnoid injection of alcohol at the level of the sixth cervical segment for relief of anginal pain. Immediately there had developed spastic paralysis of both legs and of the sphincters and partial paralysis of the arms. Necropsy, one year later, showed extensive degeneration of the columns of Goll and Burdach and of the posterior roots and cornua, together with patchy demyelination of the posterior and anterior spinocerebellar tracts and of the pyramidal tracts.

DISCUSSION

DR. ALFRED GORDON: I have observed 2 cases which were identical with that reported here. One was that of a woman and the other that of a man of middle age. Both had complained for a number of months of pain in the lower part of the back. In the case of the man, the family physician made an injection of 95 per cent alcohol. The pain was somewhat relieved but returned in a few weeks. Paresis of both lower extremities developed and gradually increased. Loss of sphincter control and paresthesia in the lower extremities also developed. Recently, the condition was as I had previously seen it. I believe that injection of alcohol is a dangerous procedure. On the other hand, perhaps a 50 per cent solution would not have done as much damage. There was no fulminating symptom in this case; the man was not totally paralyzed and was able to move around.

DR. F. C. GRANT: I have had 31 cases of subarachnoid injection of alcohol for relief of pain in my series. In 2 cases the alcohol (12 minims [0.744 cc.] in each instance) was introduced into the midthoracic region; in 1 instance partial weakness of the leg developed and persisted for almost a year. One patient who received an injection of 16 minims (0.992 cc.) into the lower lumbar sac had partial paralysis of both legs and complete relaxation of the sphincters. Relief of pain was satisfactory in 15 cases and partial in 6; in 10 cases no relief was noted, even after two or more injections. In every instance in which alcohol was injected the patient had a malignant growth, so that the effect did not need to be prolonged.

In the past ten years I have not seen loss of sphincter control follow unilateral chordotomy. Yet in 3 of 4 cases in which previous injections of alcohol in the lumbar subarachnoid space were unsuccessful and unilateral chordotomy finally relieved the pain, there was loss of sphincter control. I believe that the alcohol interferes with sphincter control on the side to which the pain is referred, and may frequently do so without relief of pain. If thereafter chordotomy is carried out, of course on the contralateral side, this may interfere with the sphincter fibers and result in complete loss of bladder and bowel control.

This is my chief complaint, aside from the recognized dangers of inaccurate injection which the authors have emphasized, with the subarachnoid route. Relief of pain by this method is never certain, and a subsequent unilateral chordotomy which would surely relieve pain may be complicated by sphincteric difficulties which this operation by itself never produces.

DR. R. A. GROFF: Although the discussion has centered around the treatment of pain, I shall answer only those questions which pertain to the injection of alcohol into the subarachnoid space. We believe that the use of absolute alcohol in the lumbar region is valuable for the relief of pain in certain instances. How-

ever, all the precautions which have been pointed out by Dogliotti, of Italy, and Stern, of New York, must be duly respected if complications are to be avoided. One of us made injections in 23 cases, with fairly good results in all. The pain was relieved for from two to three months after the injection in about 75 per cent of the cases.

I cannot say as to the probability that chordotomy, following the injection of alcohol into the subarachnoid space, will cause a higher incidence of paralysis of the rectal and vesical sphincters.

Dr. Gordon's question about the use of weaker solutions of alcohol is out of place. The principle of the injection of alcohol into the subarachnoid space is the floating character of absolute alcohol in relation to the cerebrospinal fluid. It is necessary for the alcohol to "lake" on the spinal fluid in order that the desired effect be produced. If one should use lower concentrations of alcohol, diffusion of the alcohol would take place and consequently the effect would be lost and damage done over a wider area.

Electroencephalography. DR. JOSEPH F. HUGHES.

Clinical interest in electroencephalography began with Berger's report of finding slow potentials in 2 cases of tumor of the brain (*Arch. f. Psychiat.* **100:** 301, 1933). This type of examination was first made at the Institute of the Pennsylvania Hospital in 1934 on a group of patients with schizophrenia, manic-depressive psychosis and involutional melancholia. The results of this study failed to reveal any significant difference between these patients and normal persons which could not be accounted for by the patients' lack of cooperation, inattention or distractibility. These studies were reported on by Hughes, Strecker and Appel (*Am. J. Psychiat.* **94**:1179 [March] 1938).

It is in the neurologic field that brain potentials are of the greatest diagnostic usefulness, because lesions which destroy cells in the gray matter give rise to abnormal potentials. Two years after Berger's report, Kornmüller (*Biol. Rev. Cambridge Philos. Soc.* **10**:385, 1935) and Foerster and Attenburger (*Deutsche Ztschr. f. Neurol.* **135**:277, 1935) confirmed his findings. Walter (*Proc. Roy. Soc. Med.* **30**:579 [March] 1937) succeeded in localizing tumors in 12 cases. Williams and Gibbs (Electroencephalography in Clinical Neurology: Its Value in Routine Diagnosis, ARCH. NEUROL. & PSYCHIAT. **41**:519 [March] 1939) made accurate diagnoses in a group of 50 cases by this means.

Since 1935, the electroencephalograms, made at the Institute or at the Department for Mental and Nervous Diseases at the Pennsylvania Hospital have been obtained on patients with behavior problems, epilepsy, psychoneuroses or psychoses. More recently, patients with suspected tumor of the brain and other neurologic lesions have been examined. The latter have come chiefly from the service of Dr. B. J. Alpers, at the Jefferson Medical College Hospital, and of Dr. J. C. Yaskin, at the Graduate Hospital.

The findings in cases of epilepsy may be summarized as generalized abnormal activity or localized trigger areas. This activity consists of high voltage fast spikes and slow waves, with usually a 2 or 3 or a 6 to 8 per second rhythm. These waves are from five to ten times as high as normal. Different combinations of these rhythms occur. In some cases of grand mal or petit mal tracings between attacks may be normal. Use of sedatives may eliminate or mask these abnormal rhythms. There is no characteristic tracing for the different clinical types of epilepsy.

When a behavior problem is associated with encephalitis abnormal waves may be discovered. The findings in cases of the psychoneuroses and psychoses are equivocal, as has been previously indicated. In the group of patients with tumor of the brain, accurate localization was made in each of the 10 patients who had a lesion involving the superior or lateral aspect of the cerebral hemispheres. These lesions included porencephaly, astrocytoma, meningioma and cortical atrophy (Pick's disease). Four patients suspected of having cerebral tumor, with

headaches and choked disks, gave normal electrical tracings. The subsequent clinical course showed that they did not have tumors. Two patients were reported as having tumors of the frontal lobe; air encephalograms failed to reveal any lesion. In these 2 cases the diagnosis is still uncertain.

The electroencephalogram is inaccurate in cases of lesions of the posterior fossa. Two cases of tumor of the fourth ventricle, 1 case of meningioma of the posterior fossa and 2 of 4 cases of tumor of the cerebellopontile angle were missed in the electrical examination.

DISCUSSION

DR. F. H. LEWY: The electroencephalogram promises to become a useful clinical tool in the future. At present its diagnostic value is limited. One knows empirically the typical pattern of epilepsy and the long waves in the neighborhood of tumors of the brain. Here, again, the practical help of the electroencephalogram is confined to surface tumors, which as a rule can be correctly located by older methods. So far no conclusions can be drawn from the electroencephalogram as to the degree of mental activity or dulness; for example, Gammon and I found an apparently normal pattern in a child with hydrocephalus of enormous development and a paper-thin cortex.

DR. SAMUEL B. HADDEN: Does the cellular structure of tumors make any difference in the waves observed?

DR. JOSEPH F. HUGHES: It is not possible to diagnose the type of tumor or lesion from the electrical record, as these potentials come from the pyramidal cells and their processes in the cerebral gray matter, and not from tumor cells. That the brain potentials are chiefly cell potentials is in accord with the point of view expressed by Dr. McCouch.

As to technics for placement of electrodes: Paired scalp leads are best for diagnosis of tumors and single scalp leads for diagnosis of epilepsy. The type of lead to be used can be determined from the clinical findings. In my cases of jacksonian epilepsy the foci of abnormal activity have been multiple instead of single.

The results to date in cases of tumor of the brain reveal that the electroencephalogram has been accurate in 10 cases of supratentorial tumor. These included 7 cases of tumor in the frontal lobe, 2 of tumor involving the sphenoid ridge and 1 of tumor of the corpus callosum. In contrast, 2 cases of tumor of the fourth ventricle, 1 case of meningioma of the posterior fossa and 2 of 4 cases of tumor of the cerebellopontile angle were missed. In conclusion, it may be said that the electroencephalogram is highly accurate in localizing lesions on the superior or lateral aspect of the cerebral hemispheres. This accuracy disappears in cases of involvement of the posterior fossa and is probably impaired in cases of tumor of the pituitary body or pituitary stalk or of lesions on the floor of the anterior or middle fossa.

Electrical Activity of the Cortex and Changes in Cortical Blood Flow Induced by Metrazol and Other Exciting Agents. DR. ROBERT D. DRIPPS and DR. MARTIN G. LARRABEE.

In order to analyze the mechanism by which a convulsant drug, such as metrazol, exerts its action, we have studied the effects of intravenous injection of metrazol on the functional properties of various parts of the central nervous system and on blood flow in the cerebral cortex of cats under light anesthesia induced with pentobarbital sodium or dial.

In certain experiments the response of a muscle in the hindlimb to electrical stimulation of the sensorimotor cortex was recorded. After intravenous injection of a subconvulsive dose of metrazol the amplitude of contractions elicited by cortical stimulation promptly increased (twofold or more) and then slowly returned to the control value during the next several minutes. By recording the action

potentials in the nerve to the muscle it was found that after a subconvulsive dose of metrazol impulses reached the muscle sooner after the start of the cortical stimulation and continued at a higher frequency than during the control stimulation. In other experiments evidence was obtained of an analogous action on the sensory division of the nervous system, for the amplitude of the electrical response of the sensory cortex to stimulation of a peripheral nerve was increased for several minutes after injection of a subconvulsive quantity of metrazol.

These phenomena do not appear to be secondary to the effects of the drug on the respiration or circulation. Thus, the response of a motor nerve to cortical stimulation was increased by metrazol in an animal with pneumothorax under conditions of artificial ventilation. Subconvulsive doses caused a drop in blood pressure in the anesthetized cat, which we have found to be accounted for, at least in part, by inhibition of the efferent sympathetic discharge. However, a similar drop in blood pressure produced by rapid bleeding did not increase the cortical response to peripheral nerve stimulation.

We therefore interpret the augmentation of sensory and motor responses described as meaning that metrazol facilitates transmission of impulses across the synaptic junctions in both the sensory and the motor division of the central nervous system. The convulsant action of larger doses may be due to further development of the same facilitation of synaptic transmission, to such a degree that impulses arising, for example, from the spontaneous activity of the central nervous system impinge on the motoneurons in sufficient number to initiate motor activity.

We have also found that metrazol can initiate activity in a nerve cell as well as facilitate synaptic transmission of such activity to adjoining neurons. Thus, perfusion of a sympathetic ganglion with Ringer's solution containing this drug caused a discharge of impulses into the postganglionic nerve, although the preganglionic fibers had been severed so that no impulses were entering the ganglion.

Intravenous injection of from 100 to 200 mg. of metrazol produced convulsions in the lightly anesthetized cat. As others have reported, the muscular movements were paralleled by a great increase in the spontaneous electrical activity of the sensorimotor cortex, and were followed by a period of complete suppression of all electrical activity, suggestive of the postconvulsive coma observed clinically. During this quiet period we found that the cortical response to peripheral nerve stimulation was absent; it reappeared progressively over many seconds as the spontaneous activity also returned.

In order to relate these changes in activity of cortical nerve cells to circulatory adjustments, we measured the blood flow in the sensorimotor cortex by the cooled thermocouple method. The tip of the thermocouple was also used as one recording electrode in order to observe the activity of the same region in which blood flow was measured.

The only modification of blood flow by subconvulsive intravenous doses of metrazol, and the initial response to larger doses, was a marked drop in cortical blood flow, which appeared to be a purely passive effect of the drop in blood pressure.

A convulsive dose of metrazol always produces, after the initial passive drop in cortical blood flow, dilatation of cortical vessels which greatly increases the blood flow in spite of the concurrent depression of blood pressure. The flow starts to rise soon after the beginning of the convulsion, is usually maximum during the postconvulsive depression and returns to the control value only after some minutes. The magnitude of the rise increases with the degree of cortical activity produced by various doses of metrazol. The dilatation is independent of muscular movements, as it also occurs in the curarized animal. Moreover, this vascular response does not appear to be produced by vasodilator properties of the drug itself, for in animals having a sequence of convulsions after a single injection a similar sharp rise in cortical blood flow occurred during each seizure.

We therefore conclude that the vasodilatation accompanying a seizure is produced by the intrinsic circulation-regulating mechanisms of the cortex, which

increase the blood flow to meet the increased metabolic requirements of more active nerve cells. The postconvulsive depression suggests also that even this increased circulation is temporarily unable to supply these metabolic requirements, so that the cortical neurons are for a time in what Penfield has described as a state of "functional anemia."

DISCUSSION

DR. TEMPLE FAY: Dr. Dripps has given an excellent illustration of what I have been privileged to see while exploring the cortex in the human being. In one case a portion of the convolution became involved in a vasomotor change characterized by intense flushing, followed by an attack. This vascular change was so circumscribed that it might have been covered by a 25 cent piece. Movements were focal in the arm, and these movements could be produced in and about this area by electrical stimulation. One might expect such a change in the entire field supplied by the artery or in the area supplied by a distant branch in its terminal portion, but in this instance the area was focal and was situated in the middle portion of distribution of the anterior cerebral artery.

It seems possible that local vascular changes can and do occur in the cortex which might distinctly influence local responses but which would fail to produce demonstrable chemical changes in the cerebral blood as a whole, and hence would escape detection unless actually viewed, as I have described.

This might strengthen the concept of "selective" involvement, but the idea of "selection" can be continued even further when one considers the typical pattern of a major seizure, in which extensor and flexor groups are involved but in which the rotator muscle movement escapes and, no matter how highly educated the cortex may be, the complicated movements acquired throughout life are conspicuous by their absence.

The pattern of the convulsion is the same in the infant as in the adult. This seems to me to indicate definitely a "selective" process, but a selection based on a primitive motor system which antedates the evolutionary period of more skilled, complex movement.

DR. MATTHEW T. MOORE: What was the duration of the increase of blood flow following the use of metrazol in the experimental animal?

DR. GRAYSON P. MCCOUCH: Dr. Fay's closing remarks call for a word of comment. When the motor cortex is systematically explored with stimulating electrodes a single point may be found to yield divergent, and even opposite, responses, the reaction being determined by facilitation from immediately preceding stimulation of a neighboring point. Thus, representation within the motor cortex is a mosaic of overlapping units of diverse physiologic significance. Under normal conditions, when such a physiologic group is in action its antagonists are silenced by inhibition. On the other hand, when area 4 is stimulated by electrodes or by a convulsant drug, unrelated, and even antagonistic, mechanisms are stimulated at once. Those that happen to be facilitated respond first, momentarily inhibiting the response of their antagonists. Response is followed by depression. In the meantime, the previously inhibited units recover their irritability and respond in their turn. Thus is established the alternation of clonic discharge, to be terminated only by cessation of the stimulus or by cortical fatigue. Under such abnormal, nonselective stimulation, the marvel is that coordination is maintained, however stereotyped the pattern. Such a situation would appear to be incompatible with acquired movements requiring nicety of cortical discrimination.

DR. ROBERT DRIPPS: The duration of the increase in blood flow varies considerably, and may range from two to thirty or forty minutes. These were the limits we observed, although they were not shown on the records. As far as we could determine the increase in the blood flow was coincident with the onset of the convulsion. The middle figure in one slide showed a drop at the onset of the convulsion. This was a passive response, due to a considerable drop in the blood pressure.

DR. MARTIN LARRABEE: Our first experiment was performed on a decerebrate cat, and in that animal metrazol produced strong convulsions. I should not conclude, however, that the cerebral cortex is not normally concerned in metrazol convulsions. The cortex may even play a predominant role when the central nervous system is intact. Certainly, the activity of the cortex is always markedly increased whenever metrazol causes any suggestion of a convulsive movement. I see no indication in our experiments that the convulsion may be due to a "release phenomenon," in the sense of Hughlings Jackson.

Force Required to Crush Vertebrae: Its Probable Mechanical Relation to Postmetrazol Fracture. DR. WILLIAM FURST, Norristown, Pa.

This paper attempts to evaluate the probable significance of the mechanical factors in the production of the postmetrazol vertebral fracture. The peculiar anatomic nature of the thoracic portion of the spine may explain the frequency of fracture of the fifth, sixth and seventh thoracic vertebrae. The natural convexity of this portion of the spine is somewhat increased by the thoracic intervertebral disks, which are slightly narrower in front than behind. Mobility of this region, moreover, is limited to 90 degrees in flexion and only 40 degrees in extension. The flexor muscles of the spine, therefore, apparently have a definite mechanical advantage over the extensors.

Reed and Davis expressed the belief that, since there are few muscles for producing extension of the thoracic portion of the spine, generalized severe muscular action produces extension of the cervical and lumbar portion of the spine with flexion and angulation of the thoracic region, resulting in the postmetrazol fracture localized in the latter area. Their roentgenologic studies revealed a surprising similarity in the incidences of postepileptic and postmetrazol-postinsulin vertebral fractures.

The compression force which a vertebra will withstand is probably a major factor in its resistance to fracture. The pressure necessary to crush the fifth thoracic vertebra was determined by the following method: The body of the vertebra was removed with an electric saw, defleshed and placed in solution of formaldehyde. The intervertebral cartilage was separated and the vertebra dried and placed under an electrically controlled press capable of measuring variations in pressure of within 5 pounds (2.3 Kg.). The load was applied to the flat surfaces of the vertebra. As the pressure was increased to between 250 and 275 pounds (113.5 and 124.85 Kg.) a cracking sound occurred. At this point, the bone appeared flattened, and the periphery of the superior and the inferior border of the ventral margin was separated from the body. As the load was gradually increased to between 750 and 800 pounds (340.5 and 363.2 Kg.) the vertebra cracked apart transversely. The trabeculae also appeared crushed, although the two parts retained their shape.

Although the method of preparation of the vertebrae and the circumstances of this experiment are subject to criticism, one fact appears significant, namely: The fifth thoracic vertebra when longitudinally compressed will be crushed at the peripheral portion of its superior and inferior ventral margins by a force approximately one-third that required to crush the body.

The unique construction of the vertebral body may be partly responsible for the wedge-shaped nature of the postmetrazol fracture. The trajectories described by the trabeculae of the vertebrae are prone to disruption at their centers when the vertebra is subjected to a longitudinally compressing flexion force. The middle of the ventral border of the vertebral body in its transverse axis is therefore its weakest point.

Study of the metrazol convulsion by Strauss and his associates, utilizing ultrarapid motion pictures, reveals that the seizure is tripartite, consisting of a ten second clonic stage, a ten second tonic stage and a thirty second clonic stage.

This study probably indicates an important factor in the postmetrazol fracture, which may best be illustrated by analogy with the engineering aspect of the problem of bridge construction. In computing the stress and strain tolerated by a bridge, allowance must be made not only for the total load of one hundred soldiers but also for the increased force incident to the recurrent impacts of their marching. The compression load placed on vertebrae likewise seems of less importance than the recurrent impacts of the clonic-tonic-clonic convulsion.

The fate of the intervertebral disk in the pathogenesis of the postmetrazol fracture has received scant attention. Tureen and Key suggested that, owing to direct longitudinal pressure on the vertebral bodies, there is relatively slight tendency to wedging, but the intervertebral disk may be forced into the bodies of the vertebrae. 0f 15 cases of fracture of the thoracic (ninth to twelfth) vertebral bodies from external trauma, Olin observed compression of the intervertebral disk in 88 per cent. The commonest result of this complication was the invasion of the prolapsed nucleus pulposus of the disk into the spongiosa of the vertebral body, forming a Schmorl's node. Rathmell confirmed this finding histologically in a case of postmetrazol vertebral fracture. Posterior protrusion of the intervertebral disk into the spinal canal following this type of fracture, although not yet reported, should be anticipated.

The necessity for maintaining spinal hyperextension is therefore emphasized by these observations. Counterpressure against the hyperextended spine probably offsets a compression force of between 250 and 750 pounds (113.5 and 340.5 Kg.). This may prevent crush fracture of the vertebral body, fracture of the periphery of the superior and inferior ventral margins or injury to the intervertebral disk. It is probable that pressures of about 250 pounds are related to the group II type and pressures of about 750 pounds to the group IV type of postmetrazol fractures as classified by Rathmell.

At the Norristown State Hospital I have utilized a simple but efficient means of maintaining spinal hyperextension. The patient is placed on a flat table, with hyperextension increased by a small pillow placed under the midthoracic portion of the spine and counterpressure exerted by assistants against the chin, shoulders, hips and knees. By this method I have been able to reduce the incidence of vertebral fractures to 8 per cent in 37 consecutive cases. Graves and Pignataro, using a similar means of restraint, have reported the same incidence in 187 cases. This is considerably less than the 20, 43, 47 and 50 per cent reported by other investigators.

Summary and Conclusions.—1. Several related factors probably explain the high incidence of postmetrazol vertebral fractures. 2. The relationship of mechanical factors to the production of the fracture is confirmed. 3. The peculiar anatomic nature of the thoracic portion of the spine, with its limitation in extension, may explain in part the mechanical advantage of the spinal flexor muscles. 4. The postmetrazol fracture of the thoracic vertebral body is probably as frequent as that following epileptic convulsions. 5. It is found by direct measurement that the fifth thoracic vertebra, when longitudinally compressed, will be crushed at the periphery of its superior and inferior ventral margins by a force approximately one-third that required to crush the body. 6. The unique construction of its trabeculae may predispose the vertebral body to a wedge-shaped deformity. 7. The compression load placed on a vertebra seems of less importance than the recurrent impacts of the clonic-tonic-clonic convulsion. 8. Compression of the intervertebral disks following fracture of the thoracic vertebral body may occur in about 86 per cent of cases. Invasion of the prolapsed nucleus pulposus of the disk into the spongiosa of the vertebral body, resulting in the formation of a Schmorl's node, has been demonstrated. 9. The necessity for maintaining spinal hyperextension in preventing postmetrazol vertebral fractures and complications involving the intervertebral disk is emphasized. Its use may result in reduction of fractures from 50 to 8 per cent.

BOSTON SOCIETY OF NEUROLOGY AND PSYCHIATRY

BRONSON CROTHERS, M.D., *President, in the Chair*

Regular Meeting, March 21, 1940

One Hundred Cases of a Condition Diagnosed as Acute Encephalitis: A Clinicopathologic Study. DR. ALEXANDRA ADLER.

This article appears in full in this issue of the ARCHIVES, page 541.

Androgen Excretion in the Urine in Various Neuropsychiatric Conditions: A Preliminary Report. DR. RUDOLPH NEUSTADT and DR. ABRAHAM MYERSON.

During the last decade knowledge of "sex hormones" has been so far developed that at present chemical methods, applicable in a clinical laboratory, are available for their determination. Several methods of this kind have been described, and photocolorimetric methods are being used by investigators for the determination of androgen and estrogen in urine. By these methods the combined androgenic substances, androsterone, dehydroisoandrosterone and probably etiocholane (3 hydroxy, 17 one), and the conjugated estrogenic substances, estrin, estriol and estradiol, are determined—substances to which we shall refer, for the sake of simplicity, as androgen and estrogen, respectively. Although it is impossible at present to extract all known hormones from human blood or urine, the examinations which can be carried out suffice to clarify the biologic activities which underlie certain sexual neuroses.

A standard curve, according to the different ages and sexes, was first established, and the individual results obtained were plotted against the values for the standard curve. Factors such as age, sex, amount of urine, physical strain and irradiation were taken into consideration in designating the results as "low" or "high," "normal" or "pathologic."

The first group consisted of the urine of 26 homosexual persons, 11 of whom were under our observation and showed true overt homosexuality; the other group of urines of 15 homosexual persons came to us from various other sources. Of this series, 23 showed a strikingly characteristic disproportion between the androgen and the estrogen content. This expressed itself in one of two ways: Either the androgen was low and the estrogen very high (13 cases), or the androgen was low and the estrogen high or very high (13 cases). In either instance there was a disproportionately large amount of estrogen present as compared with the androgen. We feel certain, therefore, that this disproportion is an underlying biologic cause in the majority of cases of true overt homosexuality.

Of 12 patients with impotence, 9 showed very low excretion of androgen and estrogen before treatment; in these cases the impotence was psychoneurotic, not a lack of sexual activity in patients with endogenous depressions. Six of 7 patients who masturbated had an excessively high excretion of androgen and estrogen, while the seventh patient had a normal excretion. Castrated persons and patients with Fröhlich's syndrome showed low or very low readings, while those with Simmonds' disease showed absence of "sex hormone" excretion. Patients with hypothyroidism and hyperthyroidism (14 cases) showed very low excretion; that is, in all cases in which the thyroid disorder had lasted for a long time the findings indicated severe damage to the genital and extragenital sites of formation of androgen.

Manic-depressive and schizophrenic patients have given insignificant results up to the present. In so-called involutional melancholia (6 male patients) the distribution of low and normal results was exactly the same as for a control group (6 patients) of the same age but with no psychosis. From this we may conclude tentatively that hormonal regression is nothing more than an accompanying factor in the depressive psychoses appearing in the sixth decade of life.

In the last part of the paper it is shown that ultraviolet irradiation increases formation and excretion of "sex hormones." This is shown by colorimetric measurement and by biologic controls with the chick comb–growth test. Ultraviolet irradiation constitutes a physiologic way of restoring a disturbance in hormone balance.

The general results of our hormone studies thus far indicate that urinary hormone determinations are an aid in the diagnosis of the sexual constitution of the individual person, and hence an important guide to therapy so far as type, method to be utilized and amount are concerned. Light has been thrown on pathophysiologic developments in various diseases, and interesting knowledge of certain psychophysical relations has been gained.

DISCUSSION

DR. H. B. FRIEDGOOD: One of the important things to remember in evaluating the results of this clinical investigation is the relation of the urinary androgens to androgen metabolism in the tissues. Practically nothing is known about this phase of the subject, on which preliminary experiments are being done in Callow's laboratory in England.

It is known that there are three androgenic substances in normal male urine, viz., androsterone, dehydroisoandrosterone and etiocholane (3 hydroxy, 17 one). These are all degradation products of androgen metabolism; while they show androgenic activity, they are not actually the male sex hormones secreted in the body. Testosterone has not been found in the urine, but has been isolated only from testis tissue; adrenosterone, another androgenic substance, has been found by Reichstein in the adrenal cortex. The Callows have found that injection of testosterone causes an increased amount of androsterone and etiocholane (3 hydroxy, 17 one) to appear in the urine. Where dehydroisoandrosterone comes from is not known. Presumably it comes from the adrenal cortex, because it has been found in the urine in increased amounts in patients with tumors of the adrenal cortex, both by Callow and in my laboratory.

It is of interest also to point out that Dr. Neustadt has made his assays of urinary androgen by a colorimetric method, which is based on Oesting's modification of the Zimmermann metadinitrobenzene reaction. Callow, who has made a thorough study of the relation of the colorimetric method of assay to the bioassay, found a significant correlation between the two. I have definite experimental evidence, however, of the relative inaccuracy of Oesting's colorimetric method of assay on which Dr. Neustadt's method is based. Dr. Neustadt has undoubtedly improved the method by using it in conjunction with the Evelyn photoelectric colorimeter, but I prefer to see these experiments done with a more acceptable technic.

The effect on urinary excretion of androgen of exposure of the skin to ultraviolet radiation is interesting. The colorimetric method of assay is based on the determination of ketones. It is therefore nonspecific. Are the increased amounts of ketonic substances found in the urine after irradiation really androgenic substance in the biologic sense? Dr. Neustadt's results suggest that they are. On the other hand, it is curious that irradiation of the scrotum should result in considerably larger amounts of urinary androgens than irradiation of any other part of the skin. It is well known, of course, that ultraviolet light does not penetrate the skin.

In closing, I wish to comment on the unusual feature of the curve for urinary excretion of androgen in relation to the age of the patient. There is a sharp decrease in the total androgen after the twentieth year, and this decreased level is maintained until the fiftieth year, at which time there is a sharp rise in the amount of urinary androgens. The data in the literature are not in accord with this contention.

DR. ROBERT SCHWAB: Patients with myasthenia gravis may have lowered sex desire and power. In the few patients examined by this method, I am surprised to find that values in the urinary excretion were also low, but not very low. I

am led to wonder whether treating patients suffering from severe myasthenia with testosterone in order to raise the level of the general muscular strength and well-being would be effective.

DR. RUDOLPH NEUSTADT: Every worker in this field will share some of the doubts expressed by Dr. Friedgood. However, I refrained from making the matter too complicated. On the other hand, I think that Dr. Friedgood is too skeptical. Determinations of urinary hormones are not entirely without clinical value, although one does not know to what extent one is studying only the "waste products" of metabolism. Dr. Myerson and I, in a paper published last year on the influence of ultraviolet radiation on "sex hormone" excretion (*Endocrinology* **25:7** [July] 1939), stated that the final proof would be the bioassay. Therefore, experiments on about 80 chicks were carried out, the general outcome of which has been shown here. This correlation between bioassay and colorimetric assay offers great encouragement for the continuance of our work, and we think that we have a tool of some value. This is especially true so far as the sexual constitution is concerned, in which we find an amazing coincidence between Dr. Myerson's clinical observations and the laboratory findings.

I have had no experience with the testosterone treatment of myasthenia gravis. Since testosterone exerts some influence on muscular metabolism, it may be worth while for Dr. Schwab to try this treatment. However, I am skeptical about the success of all hormone therapy I have seen thus far.

Vestibular Reactivity in Schizophrenia. DR. ANDRAS ANGYAL and DR. NATHAN BLACKMAN, Worcester, Mass.

This paper appears in full in this issue of the ARCHIVES, page 611.

BRONSON CROTHERS, M.D., *President, in the Chair*

Regular Meeting, April 18, 1940

Behavior Characteristics of Schizophrenic Children. DR. CHARLES BRADLEY and MISS MARGARET BOWEN, East Providence, R. I.

Although schizophrenic psychoses and schizoid personalities are known to occur in children, remarkably few attempts have been made to enumerate the particular characteristics which distinguish such conditions from other forms of maladjustment in childhood. At the Emma Pendleton Bradley Home a study was undertaken in an attempt to remedy this deficiency. The outstanding personality traits of 4 children with schizophrenic psychoses and 10 nonpsychotic children with schizoid personalities were compared with those of 124 children with other maladjustments, of various types. Eight behavior characteristics capable of objective description were especially prominent in the children with schizophrenic psychoses or schizoid personalities: (1) seclusiveness; (2) irritability when seclusiveness was disturbed; (3) daydreaming; (4) bizarre behavior; (5) diminution in the number of personal interests; (6) regressive nature of personal interests; (7) sensitivity to comment and criticism, and (8) physical inactivity.

The absence of dulness of emotional response in these children was in contrast to what is often noted in adults. It was possible to establish a specific definition for the terms involved in describing the eight personality traits. By noting their presence or absence in individual children a presentation of clinical behavior may be arranged on a systematic basis. Comparison of the record of one child with that of another is thus facilitated. While symptoms alone should never be made the basis of a diagnosis of schizophrenia in childhood, they are always an important factor in arriving at such a decision. The results of the present study may, therefore, clarify this aspect of the disorder.

DISCUSSION

DR. C. MACFIE CAMPBELL: I am much interested in this presentation; the analysis of the cases does justice to a syndrome which is characteristic. The clinical picture has been included in the large group of schizophrenic syndromes. The term schizophrenia must be looked on as a first approximation to precise formulation. The time will come when it can be discarded, and there will be available terms which do justice to smaller and more homogeneous groups of cases. It is unsatisfactory to have the term "schizophrenia" apply to the condition in children 7 or 9 years of age and to such dissimilar syndromes in elderly people.

From the large group of schizophrenic syndromes one can isolate a small subgroup with no florid symptoms but with indications of fundamental deterioration. The first symptom which patients with this form show in early adult life is seclusiveness. They display absence of normal spontaneity, gregariousness and response to social values.

In the authors' group of children the clinical picture is somewhat similar. Apparently in these children the inner life is extraordinarily restricted and barren; there is little evidence of special fantasies, although the patients have been studied with unusual care.

Both in the authors' juvenile group and in the somewhat older group with a similar clinical picture one may be dealing with some impersonal process involving the basic mechanisms of human nature.

DR. ISADOR H. CORIAT: In the history of psychiatry opinions concerning the age limit of schizophrenia have varied. At one time the disease was looked on as purely a disorder of puberty or adolescence; later it was shown that there are involutional types, with catatonic reactions. It seems from my clinical experience that the time of appearance of schizophrenic reactions should be pushed back before puberty. In most of the present cases the children were at a critical latent stage of libido development, which is a period fraught with danger because during this latent phase certain character types are formed on the basis of earlier pregenital drives. When conflicts arise during the period of latency, severe neuroses, sometimes with a schizophrenic coloring, and even severe schizophrenic psychoses may develop. To me, the most characteristic symptom in these cases was the regression to an earlier stage of libido development, the same type of regression which takes place in cases of more severe schizophrenia in both the adult and the involutional period. Some English analysts, particularly Melaine Klein, have reported the occurrence of schizophrenic reactions in young children. The children in her series were younger than those in the group reported on by Dr. Bradley, and the diagnosis was based principally, almost preeminently, on their negativistic behavior.

I wish to ask Dr. Bradley how malignant the schizophrenic reactions were—whether he was able to follow the patients beyond the period of puberty to determine what changes or regression took place and whether some of their reactions might be malignant rather than benign, because of the stormy latent period in which they developed.

DR. KENNETH TILLOTSON, Waverly, Mass.: I know little about schizophrenia in children, but I am actively interested in schizophrenia in adults. This is a clear and informative paper. Correlations might be made with the work on adults. The authors have presented 14 of 138 children whom they have classified according to a neat, categorical presentation of the outstanding characteristics of schizophrenia, or dementia praecox. The definitions of these categorical symptoms are clear and are familiar to those working with patients suffering from schizophrenia of a certain type. It would be invidious to try to improve on Professor Campbell's discussion on this paper, but I should like to emphasize that there are individual types within the broad framework of the schizophrenias. To me this supports the concept which is as old as the subject itself. It appears in the literature that dementia praecox of a certain type is an endogenous genetic disorder; that Dr.

Bradley should find this in children is to be expected. There are certain other types with characteristics which fit into Bleuler's concept of schizophrenia. The secondary type of schizophrenia, probably represented by the larger number of the 14 patients, Dr. Bradley covered well by saying that it possessed the characteristics of schizophrenia but that he could not diagnose it as such. Deteriorated schizophrenic subjects do not lack affect; this is entirely consistent with what one sees in adults; it may be perverse and in abeyance and may not be brought out because one does not have the persistence or the ingenuity to do so.

I wish to ask if Dr. Bradley has found any changes in the electroencephalograms of the 14 patients. If so, could he characterize them as consistent with the schizophrenic personality?

DR. PHILIP SOLOMON: I wish to make one point. I was fortunate enough to know some of the children whose cases have been reported; as I saw them, the outstanding fact was not so much that they had the characteristics mentioned but that they had them in spite of an environment which answered to an extraordinary degree the needs of children of that age. In child guidance clinics any one of these traits is seen over and over in children whom one considers essentially normal, but these characteristics clear up when one manipulates the environment in such a way as to eliminate whatever seems radically wrong. In Dr. Bradley's cases, however, the characteristics remained in spite of what was as close to an ideal environment as one could arrange outside a child's own home.

DR. CLEMENT BENDA, Wrentham, Mass.: In studying mentally deficient children one faces frequently the problem whether the children are primarily mentally deficient or whether the mental defect is due to an early psychosis. This problem has often been discussed; in particular, Dr. R. A. Greene, of the Walter E. Fernald State School, put much emphasis on the importance of juvenile psychoses. There are as yet no definite signs and criteria by which to decide this question, and I am indebted to the authors for offering some criteria for establishment of an objective diagnosis. However, I wish to ask whether the children who were reported as psychotic had been normal before they reached a certain age. In material in the state schools one usually is not able to note a period of normality between birth and the time that mental deficiency or psychotic behavior becomes obvious. One faces, therefore, the problem whether one should consider the children as psychotic from birth.

A second question is whether the children who were described as schizoid ever became schizophrenic. In my experience most schizophrenic patients have not shown prepsychotic schizoid personalities. I wish to know whether Dr. Bradley has seen a transition from a schizoid personality to schizophrenic psychosis.

DR. CHARLES BRADLEY, East Providence, R. I.: I am grateful for the discussion, which has been helpful and thought provoking. It is important for purposes of research to consider children as a group of subjects who are distinct from adolescents and adults. I have arbitrarily considered as children persons under 13 years of age who have not shown any signs of physiologic puberty. The oldest patient in my series is now 16, is definitely schizophrenic and is adjusting poorly at home. She has received insulin treatment in a hospital for mental disease since leaving the Bradley Home, but it has produced little change in adjustment. None of the other patients have so far passed through adolescence. Some of those who were described as schizoid are making a fair adjustment. I think I share the general view expressed in the literature that the prognosis for children with schizophrenia is poor.

The proportion of schizophrenic and schizoid children in my hospital experience may seem large, but that is probably because they represent severe disorders; only children with extreme maladjustments are referred to the Bradley Home, usually after all other therapeutic resources have failed.

Electroencephalograms were obtained on all the children and showed a variety of patterns. There is apparently no specific disturbance in cerebral rhythm which

accompanies schizophrenic behavior in childhood. In our opinion, any neurologic disturbance which is reflected in an abnormal electroencephalogram presents an additional factor that renders good social adjustment difficult.

The differential diagnosis of severe schizophrenia in childhood and mental deficiency is often difficult. One of my patients is now in a state school for the mentally defective and may benefit from the training which is offered, although the prognosis is doubtless poor. It is probable that most children with schizophrenia continue to have the illness through later life. Doubtless some of the schizoid children become schizophrenic later, although the adjustment of some may improve so that they go through life without acquiring an actual psychosis.

Is Intensive Vitamin Therapy Indicated for Alcoholic Polyneuritis? Dr. Madelaine R. Brown.

Abstracts of 600 cases of a condition diagnosed as alcoholic polyneuritis at the Boston City Hospital between 1920 and 1939 have been made, with emphasis on the neurologic examination and on the type and results of the therapy utilized. A selection of 250 cases, representing 260 admissions, was made. Three hundred and forty cases were not used because of a questionable diagnosis, complicating diseases or insufficient data. With the exception of 8 patients on whom a special study had been made at the Thorndike Memorial Building and 14 patients who had been discharged as unimproved after an adequate stay in the hospital, the patients were classified in four groups according to the severity of the polyneuritis. Patients representing 118 admissions between 1920 and 1929 who were given the house diet were compared with the same number admitted between 1930 and 1938 who were placed on an intensive vitamin regimen. This regimen consisted of the "high vitamin diet" prescribed at the Boston City Hospital (house diet plus fruit juice, eggnog and salad), cod liver oil and a yeast concentrate. All patients were discharged as well, improved or relieved. The average length of stay was calculated for each of the four groups in the two series.

Thirteen patients on the high vitamin regimen were given thiamine chloride and 44 liver extract parenterally. During a special experiment 8 patients were given a pint (473 cc.) or more of whisky daily plus the intensive vitamin diet. Six of the last patients remained in the hospital four times as long and 2 twice as long as those on the house diet. Of the patients who did not improve, 6 received the house diet and 8 intensive vitamin therapy.

The average time spent in the hospital by the patients suffering from alcoholic polyneuritis who were discharged as well, improved or relieved was less when the house diet alone, rather than intensive vitamin therapy, was prescribed. The economic aspect of these figures is apparent.

DISCUSSION

Dr. H. Houston Merritt: This subject is of interest to all. I think Dr. Brown would consider her report only a rough analysis because so many factors need to be evaluated. The data seem to indicate that it does not make much difference whether patients with polyneuritis are given vitamins in addition to the regular hospital diet. In group 3 vitamins could not have been expected to produce any dramatic effects, since time is needed for regeneration of degenerated nerve fibers, but this would not hold for groups 1 and 2. My experience so far has indicated that vitamins do not appreciably influence the course of alcoholic polyneuritis. The literature is full of uncontrolled reports of the "cures" of many conditions with vitamin therapy, and there is need for more critical studies, such as that presented by Dr. Brown.

Dr. James B. Ayer: I am not greatly impressed with the premise that the duration of hospital care is a good measure of the success of treatment in these cases. Too many factors enter in to make such an evaluation dependable. Dr. Brown is a careful observer, and I prefer to depend on her personal findings as

to the value of vitamin therapy for neuritis. My experience is necessarily much less than hers at the Boston City Hospital, but it is my opinion, which is in agreement with her conclusions, that vitamin therapy has not been as strikingly successful as one has been led to expect from the mass of literature.

DR. JOHN ROMANO: To my mind, utilization of the period of hospitalization, expressed in the number of days, as a criterion of success or failure of therapy is of questionable validity. All have noted that whenever a new means of therapy is introduced it leads to a more thorough scrutiny of the problem and a better understanding of the disease which is treated. There is also greater attention directed to the effects of treatment, and in many instances patients are kept for long periods, particularly in research units, in order to check the results of the therapy. In the neurologic unit of the Boston City Hospital I know of 2 or 3 instances in which patients with alcoholic neuritis and an associated Korsakoff psychosis were kept for longer period than they would have been in the previtamin era.

DR. LEO ALEXANDER: Dr. Brown has presented an extremely important and challenging paper; as is the case with every truly good paper, its value is equally great whether one accepts the author's interpretation or interprets the results in a different way.

Most will remember that the original discovery of the avitaminotic nature of alcoholic polyneuritis was made at the Boston City Hospital by Dr. George Cheever Shattuck in 1928. This was confirmed by Dr. Wechsler in New York in 1929 and by Drs. Minot, Strauss and Cobb at the Boston City Hospital in 1933. From here the discovery has spread throughout the medical world and has even reached the Far East, where under the influence of this work one has learned to recognize the avitaminotic nature of some of the so-called toxic syndromes in intestinal disease, particularly in dysentery (Alexander, L., and Wu, T. T.: *Chinese M. J.* **48**:1, 1934). It is surprising, therefore, to find a note of discouragement coming from the Boston City Hospital.

I am sure that Dr. Brown will agree that in certain cases striking improvement in alcoholic polyneuritis can be obtained by vitamin treatment. Particularly outstanding is a case which I am sure many members of the staff will remember, that of a patient who was treated at the Boston City Hospital in February 1939. However, I must agree with Dr. Brown that there are patients who do not react at all to the treatment. It is somewhat distressing to realize from Dr. Brown's studies on the material of the Boston City Hospital that on a statistical basis the cases in which the treatment was unsuccessful seem to predominate. However, before one can agree to the interpretation of this finding as evidence against the rationale of vitamin treatment of alcoholic polyneuritis, that is, against the consideration of alcoholic polyneuritis as a deficiency disease, one must rule out one or both of two explanations. The first involves the question whether vitamin treatment in all cases was carried out with sufficient completeness and thoroughness. One must admit that until recently serious obstacles were in the way of effective vitamin treatment on a large scale at the Boston City Hospital, owing to the fact that only lately could vitamin B_1 be purchased from city funds. Therefore, the staff was dependent on free supplies which several pharmaceutic houses allowed some of the services. This supply was frequently so limited that only a few patients could be given treatment of sufficient intensity in the light of recent therapeutic experience. The possibility therefore exists that the poor statistical results which Dr. Brown has so strikingly demonstrated were due in large measure to inadequate intensity of treatment.

Even if treatment had been carried out according to the present optimal standards, however, the unsatisfactory results could still be due to another factor, not involving the fundamental rationale of the vitamin treatment and the avitaminotic origin of alcoholic polyneuritis. It is conceivable that even intramuscular and intravenous administration of present vitamin preparations may not reach the diseased tissue in their most potent and active biochemical composition. There seems to be need for further biochemical investigation in regard to pharmacologic

vehicles, which may involve work on the molecular structure and experimental alterations of the molecular structure of some of the vitamins, particularly vitamin B_1.

In cases of polyneuritis of particularly long standing, in which severe and irreversible structural degeneration of the axons has occurred, a cure can be effected only by regeneration, not by recovery of the axon. In such cases therapeutic results should not be expected before sufficient time has elapsed to allow regeneration of nerve fibers. However, even in these severe forms there are usually left sufficiently numerous recoverable fibers to be benefited by intensive vitamin treatment. In reasonably early stages the frequently complete degeneration of the myelin sheaths is not attended by equally complete destruction and interruption of the axons, but is accompanied only by reversible swelling or thinning of the axons, which is recoverable with treatment.

DR. MADELAINE R. BROWN: Dr. Ayer has asked for my personal opinion based on direct observations on these patients. My experience consists of observation of many of the patients in the wards during the last ten years, and of those in the treatment clinic. For the past three years the neurologic outpatient department has had a clinic once a week devoted to therapy. Here parenteral treatment can be given and a patient followed after discharge from the hospital. I have given the patients with alcoholic neuritis the benefit of the doubt. They have had thiamine chloride intramuscularly once a week and by mouth on the other six days. Some have had liver extract intramuscularly and yeast tablets by mouth. If they abstain from alcohol they slowly improve. I have seen no case of dramatic improvement either in the outpatient service or in the wards. One difficulty is that suddenly one wakes up to the fact that one has no patients in the clinic. They have disappeared. There has been under treatment, also, a series of patients with diabetic neuritis, and it is interesting to see the difference between the two groups: The diabetic patients are lined up for treatment a half-hour ahead of time.

It has always been my opinion that there is present a third factor, in addition to the diet deficiency and the alcoholism. There is no doubt that the absence of alcohol and an adequate diet protect patients with alcoholic polyneuritis from this as yet undiscovered factor. Clinically, alcoholic polyneuritis is like arsenic polyneuritis, and no other type. In the past I have examined a number of patients with alcoholic neuritis for the presence of arsenic and have found it, but have not found it in alcoholic persons without polyneuritis or in control subjects.

Length of stay in the hospital is far from an ideal criterion, but I have a feeling that if one could observe simultaneously both the controls and the treated patients of groups 1 and 2, one would not have a measurement of improvement any more exact than the intern's opinion of when he can safely discharge an alcoholic person from a very active and crowded medical service.

I am not criticizing the work at the Boston City Hospital, for there is no doubt that large amounts of vitamins should have been tried; however, it also should be pointed out that the house diet is not only an adequate but also an excellent diet. Since this work originated at the Boston City Hospital, perhaps it is best to have any question come from that institution. There are few hospitals in this country which could offer such a large series of cases. Dr. Jolliffe, of Bellevue Hospital, has done a great deal of work on this subject, but as far as I know he has used no controls.

Neurohistopathologic Changes Resulting from Insulin and Metrazol "Treatment" in Monkeys. DR. KNOX H. FINLEY and DR. CHARLES BRENNER.

Four adult Macacus rhesus monkeys received a series of metrazol convulsions (fifteen, twenty-one, forty-five and forty-eight convulsions, respectively) during a period of several weeks. The brains of the animals, when examined microscopically, showed two types of lesions: (*a*) small foci in the cortex in which nerve

cells were missing, and in some of which there was evidence of hemorrhage, and (*b*) mild proliferation of astrocytes and hypertrophic changes of the microglia in scattered regions of the cortex.

The brains of 6 other Macacus rhesus monkeys were studied after each had been subjected to a single insulin coma of varying duration (three and a half, three and a half, four and a half, nine and one-third, fourteen and twenty-two hours, respectively). In the brain of 1 of the animals subjected to three and a half hours of coma and in the brain of the animal subjected to four and a half hours of coma there was acute damage to the nerve cells, probably of a reversible type. In the animal with nine and one-third hours of coma severe damage to the cortical nerve cells of an irreversible character resulted. In the brains of the animals with prolonged coma, of fourteen and twenty-two hours' duration, there were, in addition to severe damage to the nerve cells, dropping out of nerves cells in the cortex and an acute reaction of the glial elements. The anatomic changes in the brains of these animals indicate that a single insulin shock approaching nine hours in duration may result in permanent damage to the cortex.

In a third group, 6 monkeys were killed after receiving, over a period of several weeks, the following number of insulin comas, respectively, the average duration being two and one-half to three hours—nine, twenty-nine, thirty-one, thirty-two, thirty-three and forty. In these animals extensive damage to the nerve cells was found both in the cortex and in the basal structures. There was also a marked glial response, not only in the regions of damage to the nerve cells but also in the white matter of the cerebral and cerebellar hemispheres. Vascular changes were considered to be secondary. An attempt is made to reconstruct the pathogenesis of these lesions resulting from insulin, and evidence is brought forward that they may be due to the cumulative effect of each insulin shock rather than that any one lesion is caused by a single shock. It is stressed that even in the animals which received only nine insulin comas cortical damage of a permanent character was observed.

It is suggested that the metrazol and insulin shock therapies are justified only when the beneficial clinical results outweigh the resulting permanent damage to the brain which these studies demonstrate.

DISCUSSION

Dr. C. Macfie Campbell: With regard to the therapeutic value of the shock treatment of schizophrenia there has been great diversity of opinion. There has been a tendency to ignore the risks incurred in view of the grave prognosis usually associated with the diagnosis. One knows now from experimental work and from postmortem examination of patients that a certain price may have to be paid for the treatment. This price puts a certain limit on the heroic measures which some persons are willing to undertake.

Dr. Finley and Dr. Brenner have shown that the period of hypoglycemia must not be too long or irreversible changes will occur. In other cases, even when the animals have stood treatment fairly well, there have been loss of nerve cells and other tissue damage. The clinical improvement may be due to destruction of tissue, as in cases of lobotomy, in which a more tolerable equilibrium in the patient may be attained.

With regard to metrazol treatment, investigators in New York, on the basis of more than 1,000 cases, concluded that the condition of the patient after the treatment was rather worse than that of the control patients. On the other hand, in a paper from Japan it is stated that of patients treated by metrazol 30 per cent improved. However, if one is going to carry out this procedure and attempt to determine under what condition it will be beneficial, one must realize its definite limitations. In the present stage of investigation one welcomes the important contribution made in the paper by Dr. Finley and Dr. Brenner.

Dr. Leo Alexander: Dr. Finley's and Dr. Brenner's experimental work is important, particularly in view of its thoroughness and completeness. Dr. Sahs

and I studied a case of fatal hypoglycemia in man (Fatal Hypoglycemia: A Clinicopathologic Study, ARCH. NEUROL. & PSYCHIAT. **42**:286 [Aug.] 1939). The histologic observations in this case were similar to those which Dr. Finley and Dr. Brenner described in their experimental material. In our case the centroparietal region of the brain was the most severely involved. It is of interest to remember that Dr. Pauline Davis found the encephalographic abnormalities most striking in this region. The centroparietal region is probably particularly sensitive to the effects of venous stasis and backflow, in view of its proximity to the largest tributaries of the superior sagittal sinus.

DR. CHARLES BRENNER: I have little to add to Dr. Campbell's complete discussion. I wish to emphasize one point which Dr. Finley made. The lesions seen in these brains were scattered. None of the animals showed pathologic changes throughout the brain. Changes were observed not only in the cortex but also in the subcortical structures and the white matter. As Dr. Campbell has said, the basis for metrazol and insulin therapy is purely empiric. In view of the fact that administration of these drugs produced such damage as that seen in these monkeys, one must be quite sure that therapeutic results in human subjects are extremely good to justify a procedure as serious as this.

Book Reviews

Contributions from the Gannushkin Research and Neuropsychiatric Institute: Part 4. The Psychiatric Hospital. M. Z. Kaplinsky and S. V. Kraiz, General Editors. Editorial Board: T. A. Geyer, V. A. Grombach, S. G. Jislin, A. S. Kronfeld, M. J. Sereyski, A. V. Snejnewsky and P. E. Snessarew. Price, 13 rubles. Pp. 328. Moscow, U. S. S. R., 1939.

The authors state that among other achievements of socialism in the Soviet Union is the substantial progress made in the field of "practical" psychiatry, that is, in the treatment and care of the mentally ill. The efforts of Soviet psychiatrists of late have been centered on the reorganization of facilities and methods of treatment, rather than on purely academic problems. The main aim is to assist the victims of mental disorders in becoming useful members of the community by training and guiding them in their efforts to obtain gainful occupations after recovery. Sixteen articles are devoted to discussion of the types of modern "psychiatric hospitals" in the Moscow district and the methods of their organization. The importance of occupational therapy is stressed, and it is emphasized that without facilities for occupational therapy a psychiatric hospital is "unthinkable." The patients are encouraged to keep at their former type of work if possible, or if the mental or physical condition warrants a change they are trained in other kinds of work. A rehabilitated worker is given a proper place in the community on equal terms with others, and, because of the great demand for workers in the Union of the Soviets and the principle that every one who is able to work should be given an opportunity, there is no difficulty in finding gainful occupations for former psychiatric patients. The problems pertaining to organization of a "psychiatric hospital" and its personnel are discussed in detail. More than 90 persons, depending on the size of the hospital, make up the staff of a hundred bed hospital. There are 14 physicians; other members include clerks, nurses, attendants, cooks and laboratory help. The duties of each member, from the chief physician to the humblest attendant, are extensively outlined in tables and discussed in separate chapters. A rich bibliography (684 references to Russian and 255 to the foreign literature) and numerous tables refer to studies dealing with the care of psychiatric patients, statistics, organization of hospitals, medicolegal problems, prophylaxis and extramural psychiatric aid. The facts brought forth in this volume leave no doubt as to the real progress made by the Soviets in the field of practical psychiatry. According to the statistics of 1937, the average ratio of the mentally ill in the Moscow district was 15.7 per 10,000 inhabitants; the ratio of beds for Leningrad is given as 20 per 10,000 inhabitants. The ratio for Moscow was the next highest (the exact ratio is not given), while that for the entire Soviet Union was 3.6 beds per 10,000 inhabitants. Another interesting statement is that schizophrenia is on the decrease in the Soviet Union, while manic-depressive psychoses are on the increase, and that treatment of schizophrenia with sulfur gives as good results as any other method.

This is an instructive and interesting volume, conscientiously prepared and containing an enormous amount of information pertaining to an important phase in the life of a nation, the treatment and care of the mentally ill.

Psychiatrie. Collection des initiations médicales. By André Barbé. Price, 25 francs. Pp. 198. Paris: Masson & Cie, 1939.

This text conforms to a plan adopted for this series of books for the use of beginners in medicine; it contains less than 200 pages of descriptive material, arranged in three parts. The first part deals with the reasons for which a psy-

chiatrist is consulted; the second details the various procedures in a psychiatric examination—the anamnesis and mental, physical and biologic studies—and the third describes mental syndromes. The subject matter is easy to read, but is essentially a compendium or outline, useful mainly as a basis for rote memory. The only factor in its favor is its simplicity, clarity and brevity. To one accustomed to kraepelinian nomenclature the terms in the text appear strange. Dementia praecox and manic-depressive disorders receive no emphasis. Hebephrenia and catatonia are placed in the category of structural disease. In introducing the description of syndromes, the author writes: "In psychiatry it is not necessary to attempt to establish a rational classification, for this is impossible on etiologic, pathoanatomic, biologic or clinical grounds. Perhaps this presentation is too schematic, but it has the merit of being clear and containing what is known in psychiatry today." The book has little value for the practicing psychiatrist, and it is doubtful whether it has much value for any one. The impression created is that the text might well have been entitled: "How to learn psychiatry in several easy lessons."